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ORIGINAL ARTICLE

Impaired flow-mediated vasodilatation in Asian Indians with erectile dysfunction

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Endothelial dysfunction is the postulated link between coronary artery disease (CAD) and erectile dysfunction (ED). Brachial artery flow-mediated vasodilatation (FMD) is a non-invasive surrogate marker for endothelial function assessment. Despite Asian Indians representing a considerable global CAD burden, data on FMD and ED in these patients are lacking. Of the 225 patients undergoing coronary angiography, 72% had ED (assessed using the International Index of Erectile Function (IIEF-5) questionnaire); ED was moderate to severe in 61% of the patients. ED patients had a higher incidence of severe and diffuse angiographic CAD, a greater number of coronary vessels involved and a lower mean brachial artery FMD (6.40%±4.60% *vs.* 9.10%±4.87%, $P<0.001$) compared to non-ED patients. A progressive reduction in FMD was noted with increasing severity of ED. Impaired FMD ($\leqslant$5.5%) was twice as common in ED patients (52% *vs.* 24% without ED). Patients with impaired FMD had higher ED prevalence (85% *vs.* 62%) and lower mean IIEF-5 scores compared to those with normal FMD. Impaired FMD was a significant ED predictor independent of other risk factors (odds ratio, 2.33; 95% confidence interval: 0.59–9.23; $P=0.03$). An inverse correlation between FMD and ED severity was observed ($r=-0.22$; $P=0.004$). ED is common among Asian Indians with angiographically documented CAD. Patients with ED have impaired FMD independent of other risk factors, suggesting that endothelial dysfunction is the underlying pathophysiology. Urologists and cardiologists need to be aware of the association between ED, CAD and endothelial dysfunction.
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Keywords: Asian Indians; brachial artery flow mediated vasodilatation; erectile dysfunction (ED)

INTRODUCTION

Erectile dysfunction (ED) is a common medical condition that affects a significant proportion of males between 40 and 70 years of age.[1,2] The relationship between ED and cardiovascular diseases (CVD) has received considerable attention because they not only often coexist but also share multiple risk factors including diabetes, hypertension, hyperlipidaemia, obesity and smoking. The presence of concomitant ED is known to predict future coronary heart disease, stroke and increased mortality in both low-risk and high-risk cardiovascular patient populations, independent of conventional cardiovascular risk factors.[3–5]

Endothelial dysfunction, an important antecedent event in atherosclerosis development, has been suggested as the common pathophysiological factor between ED and CVD.[6–8] Decreased endothelial nitric oxide release and impaired nitric oxide activity result in endothelial dysfunction, which is thought to be an important atherosclerosis precursor, and impaired cavernosal relaxation, which leads to ED.[9,10] Flow-induced vasodilation is an endothelium-dependent process, and impaired response to reactive hyperaemia-induced shear stress is a sign of endothelial dysfunction. Ultrasonographic assessment of brachial artery flow-mediated vasodilatation (FMD) is a frequently used, reliable and reproducible non-invasive surrogate marker for endothelial function assessment.[11,12]

Impaired brachial artery FMD in patients with ED has previously been reported, usually in patients without associated CAD, thus demonstrating the presence of endothelial dysfunction in these patients.[13–18] However, in 'real world scenarios', because CAD and ED often occur together, it is also important to assess the relationship between impaired FMD and ED in such patients. Currently, the exponentially rising CAD trend in Asian Indians, which is often more extensive and severe than that of their Western counterparts, represents a considerable global CVD burden.[19,20] Despite this observation, there are no data regarding the endothelial function, FMD and ED in these patient populations with angiographically documented CAD. The aim of the study was to prospectively examine the relationships between FMD and ED among Asian Indian patients undergoing coronary angiography for CAD evaluation at a tertiary care referral institute in Northern India.

MATERIALS AND METHODS

A total of 225 male patients undergoing coronary angiography at our Institute were included in this study and conformed to the institutional ethical guidelines. Patients were enrolled in the study with prior written informed consent; all patients underwent routine biochemical tests including a complete haemogram, lipid profile, blood sugar and renal function tests prior to coronary angiography. The

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diagnosis of acute coronary syndrome was based on the usual definitions of clinical symptoms associated with acute myocardial ischemia, electrocardiographic changes and elevated troponin levels. Standard coronary angiography was performed in all patients through either the radial or femoral artery. Angiographic CAD was defined as a >50% stenosis diameter in any of the major epicardial coronary arteries, as measured by quantitative coronary angiography, while diffuse CAD was defined as the involvement of a >20 mm segment in a particular epicardial vessel.

Diagnosis of ED

This was established using the International Index of Erectile Function (IIEF-5) self-administered questionnaire wherein ED is assessed by a five-question scoring method, and each question is scored on a 0–5 scale. Patients were divided into groups based on IIEF-5 scores as: no ED (22–25), mild ED (17–21), mild to moderate ED (12–16), moderate ED (8–11) and severe (<7) ED.[21]

Patients with thyroid disorders, renal failure, liver cirrhosis, epilepsy, Parkinson's disease, cerebrovascular accidents, chronic obstructive respiratory disease, depression and those who had undergone pelvic, penile, urethral, or prostate surgery or those taking medication for ED at the time of presentation were excluded. Diabetes was defined by fasting plasma glucose levels $\geqslant$126 mg dl^{-1} (7 mmol l^{-1}), and hypertension was diagnosed as blood pressure BP >140/90 mmHg or patients who are already on antihypertensive medications.[22,23]

Flow-mediated dilation measurement

Endothelium-dependent brachial artery FMD was measured following reactive hyperaemia, as previously described.[24] Each subject was studied after abstaining from alcohol, caffeine, tobacco, vasoactive agents and food for 12 h before the examination. A longitudinal image of the artery was taken at rest using a high-resolution ultrasound (10.0 MHz linear array transducer; GE Vingmed Ultrasound AS, Horten, Norway) and continuously from 30 s before to 2 min after cuff deflation completing a suprasystolic compression (50 mmHg above systolic BP for 5 min of right upper arm). Diameter measurements were taken from one media/adventitia interface to the other at least three times at baseline and following hyperaemia. The mean of these readings was determined.[24] Among these readings, the maximum value of the brachial artery diameter was accepted as the reference value for dilatation, and the FMD was calculated as the percentage change in diameter compared to the baseline. An impaired FMD was defined as values $\leqslant$5.5%.[25]

Statistical analysis

All the data were analysed using SPSS (Statistical Package for the Social Sciences) v16 statistical software (SPSS Inc., Chicago, IL, USA). All data are expressed as the mean±s.d. The IIEF-5 score was rank transformed before analysis because of its skewed distribution. The *t*-test was used to compare mean values between groups, and the chi-square test was used to compare proportions between groups. Univariate and multivariate logistic regression analyses were used to estimate odds ratios using various baseline clinical characteristics as independent predictors of CAD—triple vessel CAD (TVD) or diffuse CAD extent, and presence or absence of ED and severe ED as the dependent variable. A multivariable regression analysis was used to adjust for confounding variables. All baseline characteristics, risk factors and comorbidities were analysed to determine the univariate predictors. All confidence intervals (CIs) are two-tailed and calculated at the 0.05 level.

RESULTS

The demographics of the overall patient population are summarized in **Table 1**. ED was present in 163/225 patients (72%); the degree of ED was severe in 38%, moderate in 23%, mild to moderate in 22% and mild in 17%. The mean IIEF-5 score was 14.19 (range 4–25); among those with severe, moderate, mild to moderate and mild ED, the mean IIEF-5 score was 5.79, 9.55, 14.06 and 19.04, respectively. A progressive reduction in the mean IIEF-5 score was noted in patients with single vessel, double vessel and triple vessel CAD (**Figure 1**, $P<0.001$ for each group); the mean IIEF-5 score for patients with diffuse CAD was also lower compared to those without diffuse CAD (**Figure 2**, $P<0.001$).

Patients with ED were older and had a lower body mass index (BMI), a higher incidence of diabetes, hypertension and a history of smoking (**Table 1**). There was no difference in lipid levels, past history of CAD, family history of CAD or clinical mode of presentation (stable angina and recent acute coronary syndrome) among those with and without ED. Those patients with ED also had a considerably higher incidence of multivessel CAD (either double or triple vessel disease diffuse CAD) and mean number of coronary vessels involved

Table 1 Basal demographics of the patient population

Variable	*ED present (n=163)*	*ED absent (n=62)*	P*
Age (year)	60.4±7.7	56.4±8.1	0.03
BMI (kg m^{-2})	24.2±2.9	25.9±3.6	0.03
Diabetes	45%	34%	0.02
Hypertension	57%	42%	0.03
Smoking	51%	36%	0.009
Total cholesterol (mg dl^{-1})	136.1±43.7	142.8±45.4	NS
Triglyceride (mg dl^{-1})	133.9±52.4	139.6±52.9	NS
Low-density lipoprotein cholesterol (mg dl^{-1})	74.3±33.6	83.6±40.7	NS
Very low-density lipoprotein cholesterol (mg dl^{-1})	23.6±8.5	25.1±9.6	NS
High-density lipoprotein cholesterol (mg dl^{-1})	31.5±7.3	33.2±7.6	NS
Chronic stable angina	37%	34%	NS
Acute coronary syndrome	65%	60%	NS
Double/triple vessel disease	80%	34%	<0.001
Diffuse CAD	81%	34%	<0.001
Mean no. of vessels	2.27±0.75	1.31±0.81	<0.001

Abbreviations: BMI, body mass index; CAD, coronary artery disease; ED, erectile dysfunction; NS, not significant.
* *P* mentioned are for those with and without ED.

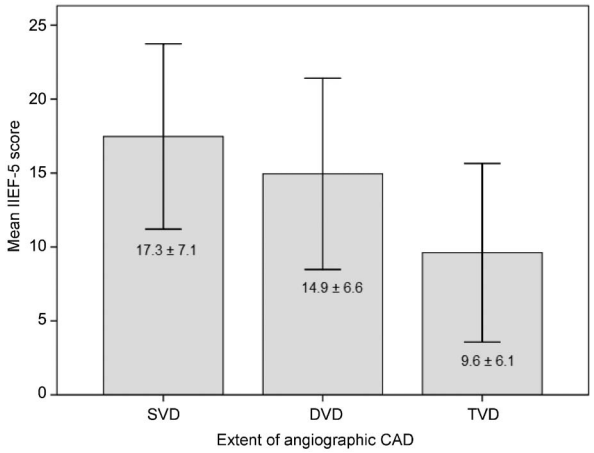

Figure 1 IIEF-5 score *vs.* angiographic severity of CAD (number of vessels involved). CAD, coronary artery disease; IIEF-5, International Index of Erectile Function. TVD, triple vessel disease; SVD, single vessel disease; DVD, double vessel disease.

(2.27±0.75 *vs.* 1.31±0.81; $P<0.001$). The prevalence of patients with TVD and the mean number of coronary vessels involved increased progressively according to ED severity. TVD patients with mild, mild to moderate, moderate and severe ED were 19.4%, 34.6%, 36.8% and 88.9% ($P<0.001$), while the mean numbers of coronary vessels involved were 1.86±0.76, 1.92±0.84, 2.00±0.82 and 2.81±0.73, respectively ($P<0.001$).

The mean FMD of the entire patient population was 7.16%±4.86%; patients with ED had a lower mean FMD (6.40%±4.60%) compared to those without ED (9.10%±4.87%; $P<0.001$). The mean FMD in patients with severe ED was also considerably lower compared to those with lesser degrees of ED (5.97%±3.58% *vs.* 7.07%±5.20%; $P=0.04$).

Patients with ED more frequently had impaired FMD as compared to those with no ED (52% *vs.* 24%; $P<0.001$). Mean FMD in patients with mild, mild to moderate, moderate and severe ED were 6.95%±4.66%, 7.02%±5.55%, 6.13%±4.72% and 5.97%±3.58%, respectively ($P=0.004$).

On comparing patients with and without impaired FMD, we observed that impaired FMD was observed in 99/225 (44%) patients (**Table 2**). There was no difference among the two groups in terms of mean age, weight, BMI, prevalence of HT, DM, lipid values, family history of CAD and clinical mode of presentation, although a higher prevalence of smoking was noted in those with impaired FMD (53% *vs.* 42%; $P=0.03$). The prevalence of multivessel CAD (65% in both groups), diffuse CAD (61% *vs.* 66%) and the mean number of coronary vessels involved (2.01±0.99 *vs.* 2.02±0.98) was also not different among the two groups.

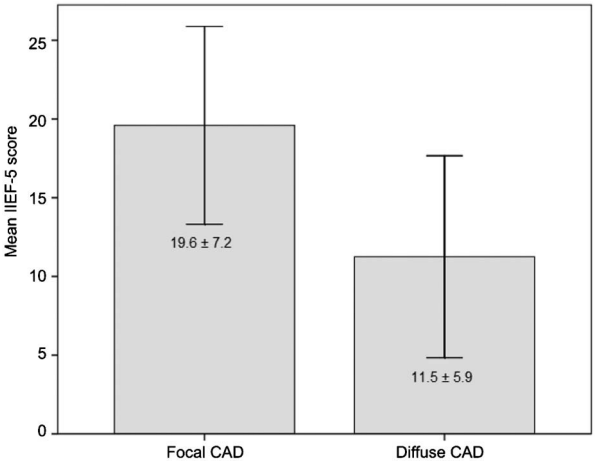

Figure 2 IIEF-5 score *vs.* angiographic severity of CAD (focal or diffuse CAD). CAD, coronary artery disease; IIEF-5, International Index of Erectile Function.

ED prevalence (of any grade) was much more common in patients with impaired FMD (85% *vs.* 62%; $P<0.001$); the mean IIEF-5 score in patients with impaired FMD was therefore considerably lower than those with preserved FMD (12.61±6.43 *vs.* 15.44±7.56; $P=0.003$). Although severe ED (IIEF-5 score $\leqslant 7$) was also more common in those with impaired FMD (31% *vs.* 24%), this difference was not statistically significant.

Table 3 describes the predictors of ED. In the univariate logistic regression analyses, age, diabetes, hypertension, smoking, FMD angiographic TVD and diffuse CAD were factors that predicted ED. In the multivariate logistic regression analyses, hypertension, smoking, angiographic TVD, diffuse CAD and FMD were the ED predictors.

Table 4 describes the predictors of severe ED. In the univariate logistic regression analyses, diabetes, smoking, FMD, angiographic TVD and diffuse CAD were predictors of severe ED. In the multivariate logistic regression analyses, angiographic TVD, smoking and FMD were the predictors of severe ED.

A positive correlation was noted between the IIEF-5 score and the absolute FMD value ($P=0.001$; $r=0.26$). We also observed a significant inverse correlation between absolute FMD value and ED severity ($r=-0.22$; $P=0.004$) (**Figures 3 and 4**).

DISCUSSION

In this study of patients (mean age 59.2±8.7 years) with a high prevalence of angiographically documented CAD, over two-thirds (approximately 72%) had ED, as categorized by the IIEF- 5 scoring system. Most patients had moderate to severe ED (61%). Patients with ED were older and had a higher incidence of conventional cardiovascular (CV) risk factors including hypertension, diabetes and smoking compared to those without ED. Patients with ED had a higher incidence of severe angiographic CAD (double or triple vessel disease), diffuse CAD and a higher mean number of coronary vessels involved compared to those without ED.

ED patients had a considerably lower incidence of endothelium-dependent FMD compared to those without ED, which reflected impaired endothelial function. Although most patients in this study had underlying CAD (as this was primarily a patient population undergoing evaluation for CAD), the FMD values in our ED patients (mean 6.4%±4.6%) compares well with those previously reported in studies comprising ED patients without associated CAD (5.1%±0.6%;[13] 6.25%±7.17%;[14] 6.01%±2.9%[15] and 4.1%±3.1%[16]). The prevalence of impaired FMD was nearly twice as high in patients with ED compared to those without ED (52% *vs.* 24%). Interestingly, despite the high prevalence of angiographically documented CAD and multiple conventional CV risk factors in the patient population, impaired FMD was absent in approximately three-quarters (76%) of patients without ED.

The impairment of FMD in ED patients noted in our study could not be attributed solely to the presence of CAD or traditional CV risk factors because patients with and without impaired FMD had a similar prevalence of hypertension, diabetes mellitus, smoking and dyslipidaemia. Moreover, the prevalence of double- or triple-vessel CAD or diffuse CAD and the mean number of coronary vessels involved were

Table 2 Basal demographics of the patient population

Variable	*Overall (n=225)*	*Impaired FMD (n=99)*	*Normal FMD (n=126)*	P*
Age (year)	59.2±8.7	58.3±9.2	59.3±9.6	NS
Body mass index (kg m^{-2})	25.7±3.4	25.2±3.2	26.1±3.6	NS
Diabetes (%)	42%	39%	36.5%	NS
Hypertension (%)	53%	56%	50%	NS
Smoking (%)	47%	53%	42%	0.03
Mean FMD (%)	7.16±4.86	3.14±2.10	9.43±3.66	<0.001
Fasting blood sugar (mg dl^{-1})	116.8±53.8	116.1±48.0	117.2±57.8	NS
Total triglycerides (mg dl^{-1})	133.0±55.2	132.2±56.5	133.6±54.5	NS
Total cholesterol (mg dl^{-1})	134.8±43.5	136.8±39.6	133.2±46.2	NS
High-density lipoprotein (mg dl^{-1})	32.6±8.2	33.1±7.2	32.3±8.9	NS
Low-density lipoprotein (mg dl^{-1})	75.5±35.6	79.0±33.6	72.9±36.9	NS
Very low-density lipoprotein (mg dl^{-1})	25.2±9.8	25.2±10.1	25.3±9.7	NS
Chronic stable angina (%)	42%	46%	44%	NS
Acute coronary syndrome (%)	58%	54%	56%	NS
Double/triple vessel disease (%)	67%	65%	65%	NS
Mean no. of vessels	2.02±0.81	2.01±0.99	2.02±0.98	NS
Diffuse CAD (%)	64%	61%	66%	NS
ED of any grade (%)	72%	85%	62%	< 0.001
Severe ED (%)	28%	31%	24%	NS
Mean IIEF-5 score	14.19±7.21	12.61±6.43	15.44±7.56	0.003

Abbreviations: CAD, coronary artery disease; FMD, flow-mediated dilatation; ED, erectile dysfunction; IIEF-5, International Index of Erectile Function; NS, not significant.
* *P* mentioned are for those with and without ED.

also similar in the two groups. Despite a similar prevalence of traditional CV risk factors and CAD extent, patients with impaired FMD had a higher prevalence of any grade of ED, including severe ED, and much lower mean IIEF-5 scores. This result suggests that ED potentially adds an incremental risk of endothelial dysfunction beyond that of CAD.

Currently, growing evidence indicates that ED is not only associated with multiple traditional CV risk factors and often coexists with CAD, but it is also a predictor of adverse cardiac events and increased mortality. The link between ED and the development of future CVD in some patients has prompted recent studies to suggest that routine screening for CVD may be rewarding in these patients; especially in those with severe ED, coexistent CVD risk factors or younger age.[26] Studies of patients undergoing coronary angiography have reported that ED is present in 50%–75% of cases, and the severity of ED is known to correlate with increased CAD severity and higher numbers of coronary vessels, which is in agreement with what was observed in our study.[27–29] Endothelial dysfunction, which is an integral antecedent event in atherosclerosis development, is thought to be the common link between CAD and ED. Most previous studies that examined the role of FMD as a marker of impaired endothelial dysfunction in ED patients have assessed patients without any associated CAD.[13–18]

Given the increasing prevalence of both CAD and ED observed in clinical practice, it is also important to study the pattern of FMD in patients with coexistent ED and CAD or other CV risk factors (which represents a 'real world scenario') as reported in the current study. However, data on FMD in ED patients and associated coronary atherosclerosis or other CV risk factors are limited and involve small numbers of patients. Abdelrahman *et al.*[30] reported impaired brachial artery FMD, lower aortic strain and higher aortic stiffness index in 30 ED patients undergoing coronary angiography; however, only 60% had CAD compared to 95% in our study of 225 patients. Elesber *et al.*[31] reported a positive correlation between coronary endothelial dysfunction (assessed by coronary flow reserve testing) and increased ED prevalence in 56 patients undergoing coronary angiography. Impaired endothelial-dependent vasodilatation has also been reported in ED patients with associated hypertension who demonstrated no other clinical evidence of arteriosclerosis.[32,33]

A multivariate analysis showed that impaired FMD is a predictor of the presence of ED independent of other CV risk factors (odds ratio: 2.33; 95% CI: 0.59–9.23; $P=0.03$). The close association between FMD and ED in our study was further highlighted by the observation of progressively lower FMD values with increasing ED severity. We

Table 3 Predictors of ED

Variable	*Univariate analyses*		*Multivariate analyses*	
	Odds ratio (CI)	P	*Odds ratio (CI)*	P
Age (year)	1.04 (1.00–1.08)	0.03	—	—
Diabetes	2.02 (0.98–4.12)	0.05	—	—
Hypertension	2.08 (1.06–4.08)	0.03	2.64 (1.06–6.61)	0.03
Smoking	2.48 (1.21–5.09)	0.01	0.45 (0.18–1.12)	0.08
FMD (%)	0.93 (0.85–0.97)	0.006	2.33 (0.59–9.23)	0.03
Angiographic TVD	9.03 (3.57–22.83)	<0.001	5.45 (1.82–16.36)	0.003
Diffuse CAD	8.29 (3.93–17.50)	<0.001	6.51 (2.59–16.33)	<0.001

Abbreviations: CAD, coronary artery disease; CI, confidence interval; ED, erectile dysfunction; FMD, flow-mediated dilatation; TVD, triple vessel disease.

Table 4 Predictors of severe ED

Variable	*Univariate analyses*		*Multivariate analyses*	
	Odds ratio (CI)	P	*Odds ratio (CI)*	P
Diabetes	3.28 (1.62–6.66)	0.001	—	—
Smoking	2.88 (1.42–5.82)	0.003	3.73 (1.22–9.32)	0.019
FMD (%)	0.93 (0.87–0.99)	0.04	0.89 (0.81–0.99)	<0.001
Angiographic TVD	74.85 (17.02–329.13)	<0.001	117.2 (19.62–700.53)	<0.001
Diffuse CAD	4.42 (1.74–11.25)	0.002	—	—

Abbreviations: CAD, coronary artery disease; CI, confidence interval; ED, erectile dysfunction; FMD, flow-mediated dilatation; TVD, triple vessel disease.

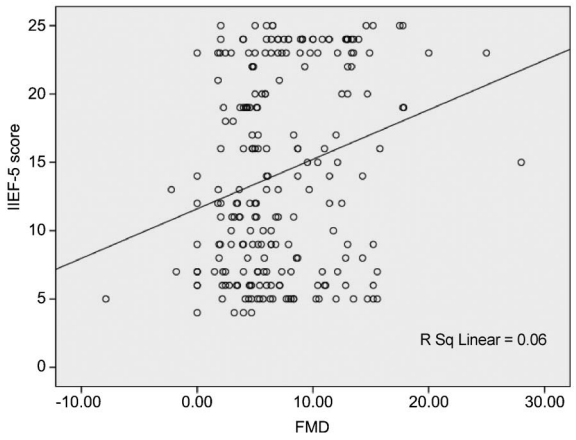

Figure 3 Correlation of FMD and IIEF-5 score. FMD, flow-mediated dilatation; IIEF-5, International Index of Erectile Function.

observed a positive correlation between the absolute value of FMD and the IIEF-5 scores, indicating that those patients with higher scores had a higher FMD. Kovács *et al.*[34] also reported lower FMD values in those patients with severe ED and a positive correlation between impaired FMD and ED; however, their study included patients with ED and no associated CV risk factors.

Our study adds to the growing evidence that endothelial dysfunction is likely a major underlying pathophysiology in ED. Endothelial dysfunction serves as the mechanistic link between ED and CAD due to reduced nitric oxide bioavailability that leads to impaired cavernosal relaxation.[34–36] In ED patients, impaired FMD and endothelial dysfunction data are also of therapeutic importance. Studies using phosphodiesterase type 5 (PDE-5) inhibitors in patients with ED have demonstrated not only an inverse correlation between the degree of impaired FMD and the required PDE-5 inhibitor dose but also sustained FMD improvement that persists even after drug therapy cessation, which reflects drug-induced changes at the cellular level.[34,37–39]

Although the brachial artery FMD measurement has operator- and patient-related limitations, an effort was made to minimize these limitations by adopting a uniform protocol and ensuring that the test was administered by an operator who was blinded to the clinical details of the patients. The impaired FMD value we considered may also be accepted as a limitation of this study, as various cutoffs have previously been described. However, we used a standard value that has previously been reported in the literature.[25] Nitrate-mediated dilatation (NMD) was not measured to study the endothelial-independent endothelial dysfunction. Although NMD has been reported to be impaired in ED patients, other studies have reported no differences in NMD between patients with and without ED.[14,15,17,30,31] Moreover, the current study focused only on the FMD that was induced by reactive hyperaemia as a surrogate marker of endothelial dysfunction. We did not perform any additional anatomical or functional evaluations of penile circulation or tests for inflammatory markers, and we did not study the role of PDE-5 inhibitors in improving the endothelial function in ED patients. Further studies are required to provide insights into these aspects.

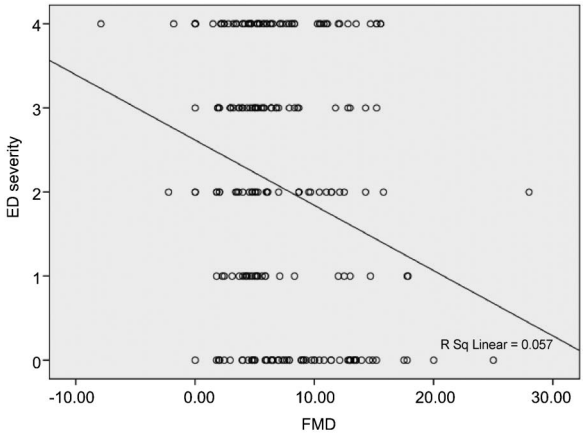

Figure 4 Correlation of FMD and ED severity. ED, erectile dysfunction; FMD, flow-mediated dilatation.

CONCLUSION

The presence of ED is common among Asian Indian patients with angiographically documented CAD, with most patients having moderate to severe ED. Patients with ED had significantly impaired brachial artery FMD, thus implicating endothelial dysfunction as an important underlying pathophysiological factor in these patients. The impairment of FMD in ED patients noted in our study was independent of traditional CV risk factors. With increasing ED severity, progressively lower FMD values were observed, and there was a significant inverse correlation between FMD and ED severity. Therefore, it is important that urologists and cardiologists account for the association of ED, CAD and endothelial dysfunction to appropriately manage these cases in clinical practice. Further studies may support the concept of ED being considered as a CAD risk factor.

COMPETING FINANCIAL INTERESTS

All authors declare that there are no competing financial interests.

AUTHOR CONTRIBUTIONS

AK, PR, TB and JK conceived of the study, participated in its design and coordination and drafted the manuscript. AK, TB and JK helped in data acquisition, analysis and interpretation. AK, TB, AS, SK, ST and NG helped in literature review and statistical analysis. AK, AS, RK and PKG made critical revisions to the manuscript regarding important intellectual contentand final approval for publication.

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