Disparity in coronary artery dimensions in diabetic and non-diabetic population undergoing quantitative coronary angiography in South India: a 2-year prospective analysis

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SUMMARY

Diabetic subjects have higher prevalence as well as increased risk for coronary artery disease than non-diabetic counterparts. The study was aimed to seek the disparity of vessel diameters among diabetic and non-diabetic patients undergoing quantitative coronary angiography (QCA). The objectives were to compare coronary artery measurements (CAM) between diabetic and non-diabetic patients and also to find the respective segment of coronary artery affected greatest among diabetics by QCA. A cross sectional study was conducted in four cities of India after procuring the sanction for the same from the ethical committee of the pre-selected hospitals of four states in India. Informed consents were obtained. Post CABG, post PCI patients and patient being diabetic for ≥5 years were also excluded from the study.

Among total sample population, non-flow limiting coronaries were seen in 1100(27.5%) cases [167 in NFL diabetic and 933 in NFL non-diabetic group]. We had 2890 (72.2%) patients with diseased coronaries. Ten segments of the coronary arteries were taken for diameter measurements namely, LMCA, LAD (O, P), DIAG, LCx (O, P), OM, RCA (O, P), RAM. These coronary diameters were indexed to body surface area (BSA) (mean diameter mm/m^2BSA). For all arterial segments both indexed and non-indexed measurements of diabetic patients with NFL coronaries had significantly ($p<0.01$) smaller arterial segments except for RCA-o. Reduced dimensions after post balloon dilatations of PCI, diffused lesions can result in increased chances for in-stent restenosis among diabetics leading to poor outcome following PCI.

Key words: Coronary artery measurements – Diabetic patients – Specific variation – Gender differences – Multi-center study

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ABBREVIATIONS:

QCA - Quantitative coronary angiography

LMCA - Left main coronary artery

LAD (O, P) - Left anterior descending artery (Ostium, Proximal part)

DIAG - Diagonal

LCx (O, P) - Left circumflex coronary artery

OM - Obtuse Marginal

RCA (O, P) - Right coronary artery

RAM - Ramus

BSA - Body surface area

INTRODUCTION

The International Diabetes Federation (IDF) estimated that 415 million, i.e., 8.8% of the world's population have diabetes mellitus (DM). Among them, type 2 (T2DM) prevail of 91% and a rise to 642 million is predicted by 2040 (Atlas, 2015; Leon and Maddox, 2015). Coronary artery disease (CAD) is a major cause of death and disability among people with T2DM (Atlas, 2015, Hertzel et al., 2010). Diabetic subjects have higher prevalence as well as increased risk for CAD than non-diabetic counterparts (Singh et al., 2013; Haffner et al., 1998). Risk of CAD can be increased in T2DM patients along with associated risk factors, such as age, hypertension, dyslipidemia, obesity, physical inactivity, and stress (Kannel, 1987). Worldwide statistics of 2007 denoted 135 million people affected with diabetes. India had the leading statistics of 40.9 million people with diabetes (Sicree, 2006). T2DM is on the verge of becoming a pandemic in India (Wild et al., 2004). Statistic predictions denote that, by the year 2025, 80.9 million people will have diabetes in India, with evidence of increased prevalence of CAD among T2DM patients (Sicree, 2006; Reddy and Yusuf,1998).

It has been reported that the phenomenon of high prevalence of diabetes reported among migrant Asian Indians (Mckeigue et al., 1991) has a wide spread from urban India as well as to rural areas (Mohan et al.,2008). Increased prevalence of diabetes in urban Indians ranges from 2.1-16% from the year 1970-2006 (Ahuja, 1979; Ramachandran et al., 1988; Ramachandran et al., 2001; Mohan et al., 2006). Evidences of endothelial dysfunction, arterial stiffness and carotid intimal medial thickness (IMT) were found to be reduced in diabetes patients compared to age- and sex-matched non-diabetic subjects (Mohan et al., 2000; Ravikumar et al., 2002). An intimal medial thickness (IMT) value is a cut-off for defining carotid atherosclerosis, and studies indicated that diabetic subjects had more incidences for carotid atherosclerosis compared to non-diabetic subjects (Mohan et al., 2000).

The left main (LMCA) coronary artery and its branches were observed as narrower in diabetic patients than in non-diabetics when the diameters of both were compared using QCA. The comparisons were done after normalizing patient's BSA by Mosteller formula between two study groups to rule out the possible bias which may have an effect on coronary artery diameter (Adil et al., 2012). Marked angiographic evidence of narrowing of coronary artery segments and long segment lesions was found in diabetic patients with CAD (Stein et al., 1995). The major arteries supplying the heart are the right coronary artery (RCA) and LMCA, with left anterior descending (LAD) and circumflex artery (LCx) for LMCA as the main branches, and the right posterior descending artery (PDA) for RCA (Aricatt et al., 2022). Evidence of narrowing of lumen diameter of coronary arteries in patients with diabetes and several factors affecting the lumen diameters have been studied previously in different countries on different populations (Melidonis et al., 1999; Gui et al., 2009; Mosseri et al., 1998; Muhammad et al., 2012).

Coronary artery diameter is one of the most important factors that affect the procedure and outcome of percutaneous coronary angioplasty (PCI), as well as coronary bypass operations (CABG) (Saikrishna et al., 2006). Post angioplasty studies among diabetic patients marked an increased risk of progressive CAD and coronary artery re-stenosis after stent implantation. The predictors of in-stent re-stenosis were decreased dimensions of coronary arteries, long segment lesion, and decreased body mass index (Moses et al., 2004; West et al., 2004).

Currently, there is no other multi-center study with international recognition among South Indian population regarding the comparison between coronary dimensions between diabetic and non-diabetic population. The study was aimed to seek the disparity of vessel diameters among diabetic and non-diabetic patients undergoing quantitative coronary angiography (QCA). The objectives under consideration were to compare coronary artery dimensions between diabetic and non-diabetic patients and also to find the respective segment of coronary artery most greatly affected among diabetics by QCA.

MATERIALS AND METHODS

Study population

A cross-sectional study was conducted in four cities of India. Hospitals were purposely selected according to the number of cardiac patients identified by them. The age of the study subjects was given a cut-off at 75 years due to marginal benefits marked during the follow-ups. Hence, a conservative approach is proven to be appropriate for the above-mentioned age, which itself indicates a poor prognosis with an average yearly mortality rate of 33-35% (Azad and Lemay, 2014). The inclusion criteria were all patients who undergo percutaneous coronary angiographic procedure due to abnormalities in the normal cardiac parameters after obtaining their informed consent. We divided the study population into two groups. Patients who were known for more than five years diabetic or were taking oral hypoglycemic or insulin therapy were enrolled in diabetic group. In non-diabetic group patients had no previous history of diabetes mellitus or patients with a controlled (an ideal glycated hemoglobin levels (HbA1c) of 48 mmol/mol (6.5%) or below) diabetic history less than five years (Srinivasan et al., 2016). Diabetic history was confirmed when patient is taking oral anti hypoglycemic drugs, insulin or recent fasting blood sugar (FBS >126 mg/dl) on two consecutive occasions. Lipid levels were obtained from hospital laboratory.

Exclusion criteria were patients with a previous history of CABG and recanalized normal looking coronary arteries with or without in-stent restenosis coronary arteries as well as patients being diabetic for five or more than five years for assessing non flow limiting (NFL) coronary artery dimensions (Srinivasan et al., 2016). The sample size was estimated by consulting a statistician and using the statistical software G* Power 3.0.10 and a 1100 NFL patients among total sample population of 4000 consecutive patients were included in the study by convenience sampling [167 in NFL diabetic and 933 in NFL non-diabetic group]. All ethical principles for human research were followed and Ethical approval was obtained from the Institutional Ethics Committee of all the hospitals from which data were collected.

Database pooling and statistical analysis

i. LMCA and RCA along with its main branches were assessed for the vessel morphology at the ostium (o) and proximal (p) segment among normal cases by stenosis analysis program. Ten segments of the coronary arteries were taken for diameter measurements namely, LMCA, LAD (o, p), diagonal (DIAG), LCx (o, p), obtuse marginal (OM), RCA (O, P), ramus (RAM). This program had incorporated an automated coronary analysis package of the Innova 2100 IQ Cath at an AW4.4 workstation or of the Siemens QCA – Scientific coronary analysis. The gender-wise categorization of the data was done to denote the mean differences in the artery measurements.

ii. Patient's anthropometric measurements were done using the fore mentioned relevant equipments. Body mass index (BMI) and body surface area (BSA) were calculated. BMI was calculated by the relevant formula weight in kilograms divided by the square of height in meters. BSA was calculated from patient's height and weight measurements using Mosteller's formula. The diameters of the ten segments of coronary artery from angiogram study samples were indexed (adjusted) to BSA (mean diameter mm/m^2BSA).

Calibration assessments from QCA (Hermiller et al., 1992) systems were carried out by the same method in which the coronary catheter was employed for angiography procedure. This was used as calibrating the object by automated edge detection technique resulting in corresponding calibration factors (mm/pixel) and the vessel contour were detected by operator independent edge detection algorithms. Angiographic views were selected for calibration assessment by minimizing the foreshortening of the coronary segments by separating them from adjacent intervening structures. Confounding variable was controlled by matching characteristic of the two groups such as age, gender, BMI and BSA. All QCA images were also reviewed by two cardiologists from each center for the definition of normal vessels and for the subsequent quantitative analysis by the double blinding method. Both the observers from each center were blinded regarding the patient identity, and interobserver variability was accounted during statistical analysis, and bias was controlled. All information was recorded on a standard proforma. All arterial dimensions were compared between the diabetic (N=167) and non-diabetic group (N=933) using Welch's t-test. Statistical analysis of the present study was done using GraphPad Prism v9.

RESULTS

Based on QCA analysis, among total sample population, NFL coronaries were seen in 1100 (27.5%) cases (167 in NFL diabetic and 933 in NFL non-diabetic group). We had 2890 (72.2%) patients with diseased coronaries. Physical and demographic parameters were assessed. The mean age of the patients was 54.50 ± 5.5 vs. 55.9 ± 7.7 years (range 30-75 years) between the diabetic and non-diabetic groups. BMI and BSA of the samples were calculated. Mean BMI in diabetic and non-diabetic groups was 26.9±2.5 vs. 25.2±3.5 kg/m^2 (range 33.30-21.26 kg/m^2). Mean body surface area (BSA) was 2 ± 0.09 m^2 vs. 1.82 ± 0.13 m^2 (range 2.1-1.42 m^2) in diabetic and non-diabetic groups.

For all arterial segments, both indexed and non-indexed measurements of diabetic patients with NFL coronaries had significantly ($p<0.01$) smaller arterial segments compared to the non-diabetic group with NFL coronaries except

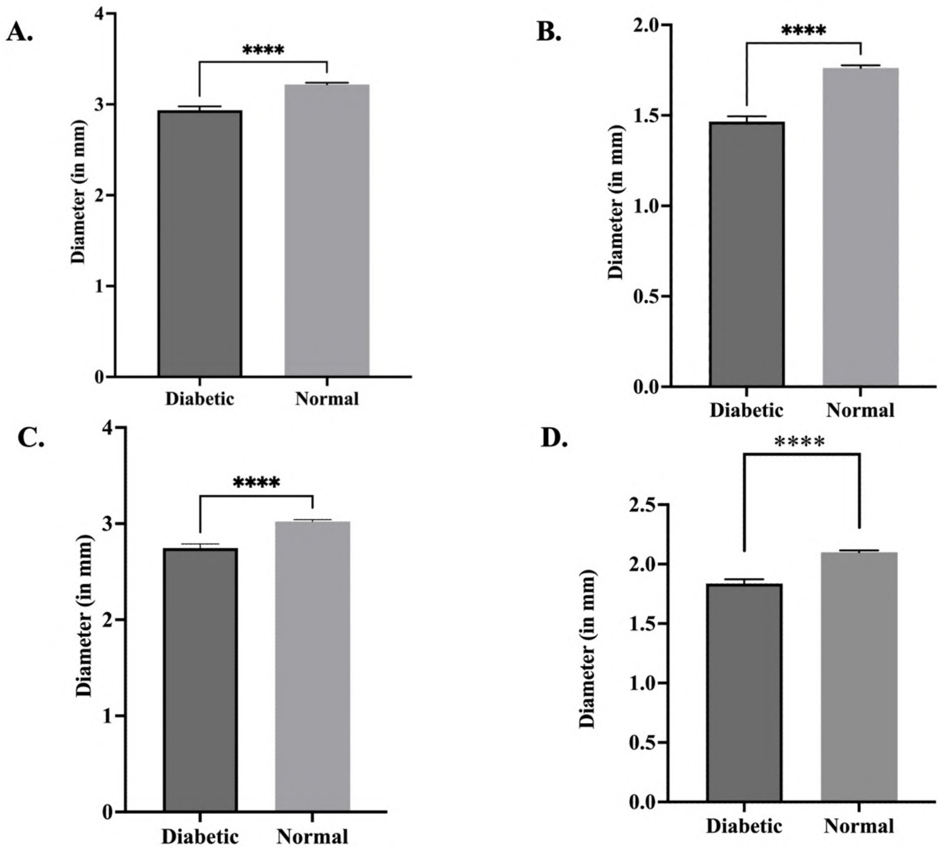

Fig. 2.- Difference in arterial dimensions between diabetic and non-diabetic patients. **A**: Difference in diameter for LAD-p. **B**: Difference in diameter for DIAG. **C**: Difference in diameter of LCX-p. **D**: Difference in diameter of OM.

Welch's t-test was performed between the between diabetic and non-diabetic patients and p-value<0.05 was considered significant. **** designates p-value <0.0001

Table 1. Differences in non-indexed coronary arterial dimensions between diabetic and non-diabetic patients.

Sl.no.	CAS	Mean diameter among NFL diabetic patients (N=167)		Mean diameter among NFL non-diabetic patients (N=933)		MD +/- SEM	Welch's-t-value	p-value
		n	CAM (mm)	n	CAM (mm)			
1.	**LMCA**	167	3.97± 0.64	927	4.16 ± 0.69	0.19 ± 0.05	3.55	0.0005
2.	**LAD-o**	167	2.95± 0.59	930	3.18 ± 0.62	0.22 ± 0.05	4.53	<0.0001
3.	**LAD-p**	167	2.94 ± 0.56	929	3.22 ± 0.59	0.28 ± 0.04	6.02	<0.0001
4.	**DIAG**	167	1.46± 0.39	912	1.76 ± 0.44	0.29 ± 0.03	8.91	<0.0001
5.	**LCX-o**	167	2.88 ± 0.67	933	3.04 ± 0.62	0.16 ± 0.05	3.02	0.0028
6.	**LCX-p**	167	2.75 ± 0.55	931	3.02 ± 0.62	0.27 ± 0.04	5.84	<0.0001
7.	**OM**	166	1.84 ± 0.46	915	2.10 ± 0.50	0.26 ± 0.03	6.64	<0.0001
8.	**RCA-o**	167	3.02± 0.75	917	3.15 ± 0.66	0.12 ± 0.06	1.97	0.0492
9.	**RCA-p**	167	2.78 ± 0.67	926	3.05 ± 0.65	0.27 ± 0.05	4.93	<0.0001
10.	**RAM**	----	----	102	2.25 ± 0.49	----	----	----

The CAM's been taken based on QCA reports and is represented as mean difference± Standard error mean of the diabetic and non-diabetic patient samples.
Statistical test used: *Welch's-t test.* p<0.001[***]indicates very highly significant difference, p<0.01[**]indicates highly significant difference, p<0.05[*]indicates significant difference, p>0.05 indicates no significant difference between non- indexed NFL CAM of diabetic and non-diabetic patients.
Abbreviations: CAS – Coronary artery segments, N- samples, n- number of samples were CAM was measurable out of total N, CAM – Coronary artery measurements, LMCA - Left main coronary artery, LAD (O, P) - Left anterior descending artery (Ostium, Proximal part), DIAG - Diagonal branch of LAD, LCx (O, P) - Left circumflex coronary artery (Ostium, Proximal part), OM - Obtuse Marginal branch of LCx, RCA (O, P) - Right coronary artery (Ostium, Proximal part), RAM – Ramus branch of coronary artery, QCA- Quantitative coronary angiography.

for RCA-o, where the mean difference between the two groups was not statistically significant (Table 1).The most striking difference between the two groups were observed for LAD-p (mean difference=0.28 mm, t= 6.023, P<0.0001, Fig. 2A), DIAG (mean difference=0.3 mm, t= 8.906, P<0.0001, Fig. 2B), LCX-p (mean difference=0.28 mm, t= 5.849, P<0.0001, Fig. 2C), and obtuse marginal (mean difference=0.26 mm, t= 6.641, P<0.0001, Fig. 2D).

Gender-wise analysis of coronary artery dimensions in the present study showed that, except for the OM branch of LCx and RAM branch of LCA, all other eight segments taken for analysis had significant differences between the coronary artery measurements (CAM) among males and females in both diabetic and non-diabetic groups. The differences were highly significant (p < 0.001). Consistent with the previous studies, we found that men are highly significantly more prone to diabetes than women (Fig. 1). However, this difference disappeared when diameters were indexed to BSA in both groups. The diameters of the normal non-indexed CAS were not measurable in certain segments due to anatomical peculiarities.

DISCUSSION

Diabetic subjects have higher prevalence, as well as increased risk for CAD than non-diabetic counterparts (Singh et al., 2013; Haffner et al., 1998). Low control of diabetes and hypertension has been reported in a study in India (Shashank et al., 2008). The improved awareness and enhanced treatment can control cardiovascular risk factors in participants with known diabetes (Brown, 2013; Gupta, 2014).

CAD in diabetic patients is found to be more severe and follow a more diffused pattern than non-diabetics (Melidonis et al., 1999; Gui et al., 2009). This could be accounted for in various pathophysiological mechanisms in diabetic patients such as hyperglycemia, hyperinsulinism and insulin resistance (Melidonis et al., 1999). In addition, narrowing of coronary artery should also be viewed as an important factor for the increased prevalence of CAD among diabetics. Although a number of prior studies have concluded that the disparity in coronary artery diameters between diabetics are non-diabetics is significant, there have been contradictory opinions regarding this concept as well. In the present study, there was no significant difference in the mean ages, BMI and BSA between the diabetic and non-diabetic groups. This is similar to the studies of Melidonis et al.(1999), and Gui et al (2009).

Angiographic comparison of different segments of the coronary artery revealed a tendency towards narrowing of artery diameters among diabetic patients with CAD (Stein et al., 1995). In the present study, all arterial segments of diabetic patients have significantly (P<0.01) smaller arterial segments compared to the NFL non-diabetic group, except RCA-o segment, where the mean difference between the two groups was not statistically significant. This contradicts the postulated theory that the predominance of stenosis in RCA can be due to the sluggish blood flow which coexists in RCA in comparison to other vessels, and the increased plasma viscosity among diabetics. The present study reports the severity of stenosis is the same for both left and right systems of coronary in patients with diabetes. In contrast, few authors from different countries have found the RCA to be significantly more frequently involved towards narrowing of artery diameters among diabetic patients with CAD (Adil et al., 2012; Melidonis et al., 1999; Gui et al., 2009; Mosseri et al., 1998; Kabir et al., 2017).

There is also evidence of smaller luminal diameter of the LAD among diabetics (Adil et al., 2012; Gui et al., 2009; Mosseri et al., 1998; Muhammad et al., 2012; Kabir et al., 2017) and distal LCx (Adil et al., 2012). The present study also indicates that the most striking differences in artery dimensions between the NFL diabetic and NFL non-diabetic group were observed for LAD-p (mean difference=0.28 mm, P<0.0001) with its DIAG branch (mean difference=0.3 mm, P<0.0001). In contrast, however, in a Greek Caucasian population, no statistically significant difference in vessel diameters between diabetics and non-diabetics for all segments of LAD was found (Melidonis et al., 1999). We had differences in artery dimensions between the NFL diabetic and NFL non-diabetic group of LCX-p (mean difference=0.28 mm, P<0.0001). However, some studies indicated the proximal LCx dimensions in diabetics and non-diabetics had no statistically significant difference between

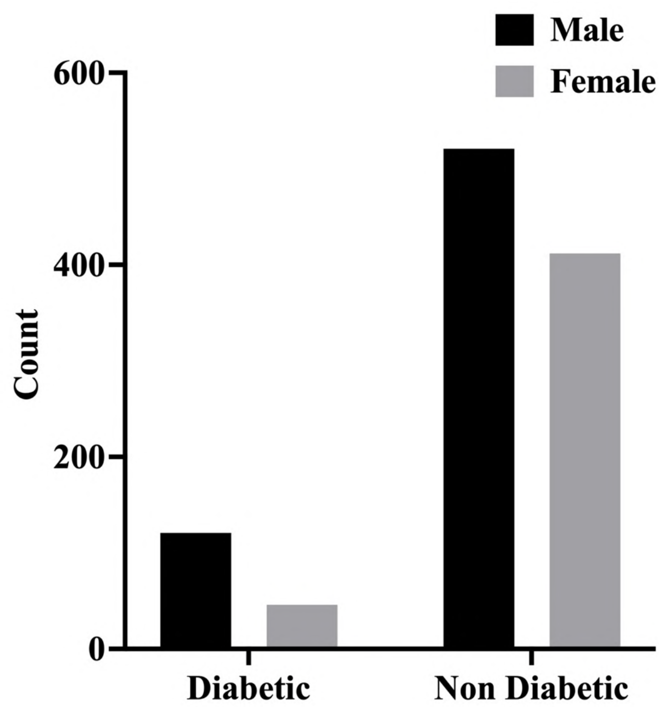

Fig. 1.- Gender specific difference in coronary arterial dimensions between diabetic and non-diabetic patients.

the two groups (Melidonis et al., 1999; Muhammad et al., 2012; Pajunen et al., 1997).

Gender-wise analysis of coronary artery dimensions in the present study showed that except for the OM branch of LCx and RAM branch of LCA, all other eight segments taken for analysis had significant difference between the CAM among males and females in both diabetic and non-diabetic groups. In general, the CAM of the male patients was greater than females in both LCA and RCA systems. However, this difference disappeared when diameters were indexed to BSA in both diabetic and non-diabetic groups. Similarly, an important observation of most QCA procedures involving coronary artery dimension analysis has revealed that women have smaller CAM compared to men (Yang et al., 2006; Raut et al., 2017).

Coronary dimensions vary throughout its length giving rise to different vessel diameters, a reference data could not be applied for comparison totally. Thus, the reduced CAM projects on its therapeutic implications, especially during revascularization procedures like CABG and PCI in diabetic patients. Reduced dimensions after post balloon dilatations of PCI, diffused lesions and prerequisite of longer stents can result in increased chances for in-stent re-stenosis and enhanced frequency of CAD among diabetics leading to poor outcome following PCI (West et al., 2004; Pajunen et al., 1997; Alonso, 2002; Fallow and Singh, 2004; Aronson and Edelman, 2010).

CONCLUSION

For all arterial segments, both indexed and non-indexed measurements of diabetic patients with NFL coronaries had significantly smaller arterial segments compared to the non-diabetic group with NFL coronaries except for RCA-o, where the mean difference between the two groups was not statistically significant.

Limitations: We could not correct the CAM of the present study for the presence of left ventricular hypertrophy, which would have enhanced the study results.

AUTHOR CONTRIBUTIONS

All authors hereby declare that their contribution was equal towards the formation of the manuscript.

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