

# Early Screening for Coronary Artery Disease is Needed in South Asian Indian Immigrants with Type 2 Diabetes

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## Abstract

**Background:** South Asian Immigrants (SAIs) are the second fastest growing Asian immigrant population in the US, and at a higher risk of type 2 diabetes (diabetes) than the general US population. Coronary Artery Disease (CAD) is the principal cause of mortality globally, particularly in diabetic subjects. In this study, we sought to determine the; 1) distribution of risk factors for CAD in diabetic and non-diabetic SAIs; and 2) presence of sub-clinical CAD in diabetic and non diabetic SAIs in the US.

**Methods:** 213 first generation SAIs subjects were recruited and broadly divided into two subgroups; 35 diabetics and 178 non diabetics. Their risk factors for CAD were compared. For sub-clinical CAD assessment, Common Carotid Artery Intima-Media Thickness (CCA-IMT) was used as a surrogate marker for atherosclerosis. For CAD diagnosis, Exercise Tolerance stress Test (ETT) was performed.

**Results:** Both diabetics and non diabetics SAIs in general, share a very heavy burden of CAD risk factors. Hypertension ( $p=0.003$ ), high cholesterol ( $p<0.0001$ ) and family history of diabetes ( $p<0.0001$ ) was significantly associated with diabetes. Presence of sub-clinical CAD was also higher in diabetics as compared to non diabetics (63% Vs 52%). 45% of diabetics (who were not previously diagnosed with CAD) were found to be ETT positive for CAD ( $p<0.0001$ ).

**Conclusion:** CAD risk factors and sub-clinical CAD are more prevalent amongst diabetic SAIs. Early screening and aggressive treatment for risk factor reduction in SAIs is the key to combating the increasing incidence of CAD. Larger prospective trials are required to confirm these study findings.

**Keywords:** Coronary Artery Disease; South Asian Immigrants; Type 2 Diabetes; risk factors; incidence

## Introduction

The prevalence of Type 2 Diabetes (henceforth, diabetes) worldwide was about 2.8% in 2000 and is projected to be 4.4% in 2030 [1-3]. India leads the world with the largest number of diabetic subjects, earning the dubious distinction of being termed the “diabetes capital of the world”. According to the Diabetes Atlas 2006 published by the International Diabetes Federation (IDF), the number of people with diabetes in India, currently around 40.9 million, is expected to rise to 69.9 million by 2025 [2-5]. Many studies have reported high rates of diabetes and Coronary Artery Diseases (CAD) among South Asian immigrants (SAIs-people from the Indian subcontinent- India, Pakistan, Bangladesh, Sri Lanka, Nepal, Bhutan) worldwide. Studies in the United Kingdom (UK) have found that SAIs’ risk of CAD death is as high as 40% above whites’, and they have a 2- to 4-fold higher incidence of diabetes [2-4]. Recently, the South Asian Association for Regional Cooperation (SAARC) reported that mortality and morbidity due to diabetes and Cardiovascular Disease (CVD) are higher in expatriate South Asian populations than in any other expatriate ethnic group worldwide [6-8]. Diabetes is a major problem among South Asians still living in Asia, as well as among SAIs who have migrated to other countries. A recent study on SAIs in the US found a diabetes prevalence of 22.5% in men and 13.6% in women [9].

The principal cause of mortality globally, particularly in diabetic subjects is CAD, as their CAD mortality risk is equal to that of subjects without diabetes who had a previous episode of myocardial infarction [9]. Metabolic syndrome predisposes patients, especially women to CAD, stroke, and diabetes [10]. Insulin resistance is postulated as a central feature of the metabolic syndrome, culminating in atherosclerosis, diabetes and CVD; a pathway potentially accelerated by migration/urbanization.

In the US, SAI population has doubled in the past decade to more than 3 million [3,9,11]. SAIs are the second largest Asian immigrant population in the US and South Asian Immigrant Indians (SAIn), a subgroup born in India, are one of the three largest Asian-American subgroups, comprising 16.4% of the total Asian population [11,12]. In spite of that, data on CAD among diabetic SAIn are limited. Since diabetes is high in SAIn and to our knowledge, no previous study has reported the incidence of CAD in diabetic SAIn population; we sought to determine the prevalence of CAD risk factors in diabetics and non diabetics as well as the incidence of CAD in diabetic SAIn living in the State of Georgia, US, which is home to a very large South Asian Indian population. We have also assessed the prevalence of sub-clinical CAD in both diabetes Vs non diabetic groups using common carotid artery Intima-media thickness (CCA-IMT) as a surrogate marker for atherosclerosis.

## Methods and Study Design

### Study was approved by IRB board of the Medical College of Georgia

Using a cross-sectional study design, a total of 213 first generation

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SAIns were randomly recruited from Hindu Temples, major businesses and other organizations in Augusta and Atlanta, the two largest cities of Georgia. Study information was made available by distributing flyers in the temples and announcements through local newspapers outlining the purpose, rationale, and design of the study. Written informed consent was obtained. Information on socio-demographic status, ethnicity (based on spoken language), personal lifestyle characteristics, as well as traditional and specific CAD risk factors was obtained for both diabetic and non-diabetic groups. Twelve-hour fasting blood samples were collected for measurements of highly sensitive C-reactive protein (hsCRP), complete lipid profile, fibrinogen activity, homocysteine, lipoprotein a (Lpa), Apo A-1 and insulin levels. We also assessed sub-clinical CAD using CCA-IMT as a surrogate marker for atherosclerosis.

### Exercise stress test

Due to limited funding, exercise tolerance test (ETT) was done only on diabetic subjects without known history of CAD in order to determine the incidence of CAD in this group. Standard Bruce protocol was followed for the stress testing [14-15]. The exercise goal was to achieve at least a target heart rate of 85% of maximum predicted for age [14]. The test could also be terminated early at the discretion of supervising physician if a subject had any significant symptoms like chest pain, shortness of breath, sustained arrhythmias, or hemodynamic or ST-segment changes[15]. ETT was considered positive for ischemia in the presence of exercise induced 1 mm horizontal or down sloping ST-segment depression 80ms from the J point. ETT was interpreted by a cardiologist.

### Carotid ultrasound doppler

IMT is defined by Pingoli and colleagues as the distance from the leading edge of the lumen-intima interface of the far wall to the leading edge of the media –adventitia interface of the far wall [16]. B-mode ultrasound scanning of bilateral CCAs was performed by a trained non-invasive vascular ultrasound technician at study clinic at the Medical College of Georgia, using SonoCalc™ IMT machine (SonoSite, Inc Bothell, WA) with a 7.5 MHz linear array transducer. Both CCAs were scanned in supine position. A total of eight images were obtained (four on each side), 1 cm proximal to the carotid bulb using an anterior approach. ECG leads were placed to obtain end-diastolic measurements. Images were recorded and stored on a disk. The CCA-IMT approach for IMT measurements was preferred because the CCA-IMT is reproducible and predictive of future cardiovascular events, and the data collection is more complete than other non-invasive markers [17-19]. Measurements of the internal carotid and bifurcation segments tend to have many more missing values [18]. The Mannheim Intima-Media Thickness Consensus suggested that measurement of the common carotid artery is ideal[20].

Any focal thickening of the intima-media complex or carotid plaque though documented, but was not included in the analysis. A cardiologist, who was blinded to participants' identities and clinical information, analyzed stored images by using automated edge detection technology (SonoCalc™ IMT). Measurement of the far wall of the carotid artery was preferred, since studies comparing ultrasound measurements with histology suggest that far-wall CCA-IMT measurements are more indicative of the true thickness of the arterial wall[21]. Near-wall CCA measurements, in comparison, are limited by their dependence on the axial resolution, gain settings of the equipment used and show greater variation between repeated measurements[22-24]. Participants with values greater than 0.80 mm were considered to be IMT positive. Previous epidemiological studies

suggest that a value of IMT at or above 0.80 mm is associated with a significantly increased absolute risk of CAD [24]. In this study CCA-IMT values of 0.80 mm or more were considered abnormal. CCA-IMT values were adjusted for age as age can influence IMT [24]. We did not include carotid plaque in this study.

### Statistical analysis

The data management and statistical analysis was performed using Windows based SPSS software, version 9.1 of the SPSS system. A detailed statistical analysis was conducted to explore the major relevant variables of the 213 participants. Baseline socio-demographic characteristics and lab measures were summarized by frequency distributions and percentages for qualitative measures and means and standard deviations for quantitative measures. Maximum likelihood estimates and asymptotic 95% confidence intervals were calculated for the prevalence of disease/diagnosis outcome measures. Bivariate tests of association were performed simple logistic regression. Multiple logistic regression models were used to assess the relative importance of variables found to be significantly associated with the outcome from the bivariate assessments. All statistical tests were two-sided and performed at the 0.05 level of significance.

### Results

The total sample consisted of 213 participants; subjects were categorized into two subgroups on the basis of diabetes: 35 diabetics and 178 non diabetics. CCA-IMT was performed on 46 individuals who provided consent; 19 diabetics and 27 non diabetics.

The mean age of subjects was 51±10.63 years with an almost equal number of males and females (Table 1). As per information from the medical history questionnaire, the prevalence of CAD was 11.2%. The history of diabetes, hypertension, smoking, and high cholesterol (≥ 200 mg/dl) was 16.8%, 21.5%, 2.3% and 36.4% respectively. Approximately 65% participants reported having physically active lifestyles. Family history of CAD and diabetes was 41.12% and 49% had two or more

Patient's characteristics	# of Patients	Percentages (%)
<b>Age Sex</b>	213	†50.99±10.63‡(Mean)
Male	105	49.53
Female	108	50.47
<b>Prevalence of CAD* and its determinants</b>		
CAD (already known)	24	11.21
¥CCA-IMT on examination	46	21.5
Type 2 diabetes	35	16.82
**Hypertension	64	29.91
Cholesterol (≥ 200mg/dL)	78	36.45
Smoking	5	2.34
Physically active	140	65.42
Family History of CAD	88	41.12
Family history of T2D	105	49.07
<b>***Age adjusted CAD risk factors</b>	N=152	
Two Risk factors	68	44.74
Three risk factors	16	10.52
Four risk factors	10	6.57

†Mean

‡Standard Deviation

\*\*Defined by Joint National Committee VI criteria

\*Coronary Artery Disease

¥ Common Carotid Artery Intima Media Thickness

\*\*\* (male ≥ 40, female ≥ 50)

Table 1: Characteristics of patients (n=213).

Risk factors	% of Diabetics (n = 35)	% of non Diabetics (n = 178)	p-value
Hypertension	37.1	15.7	0.003
High Cholesterol ( $\geq 200\text{mg/dL}$ )	54.3	24.7	<0.0001
Smoking	5.7	1.7	0.190
Physical inactivity	40.0	33.7	0.475
Family history of diabetes	77.1	43.8	<0.0001
Family history of CAD	48.6	39.9	0.340

\*Coronary Artery Disease

Table 2: Prevalence of CAD\* risk factors among Diabetics and non Diabetics.

Tests	Diabetics		Non Diabetics		P value
	Total (n=35)	%	Total (n=178)	%	
CCA-IMT positive ( $\geq 0.8$ )	12/19	63.1	14/27	51.8	0.18
†ETT positive	10/22	45%	-	-	**<0.0001

\*Fisher exact Test

\*\*Coronary Artery Disease

‡Common Carotid Artery Intima Media Thickness

†Exercise Tolerance Test / Stress Test

Table 3: Newly diagnosed \*CAD and ‡CC-IMT in Diabetics Vs non-diabetics.

CAD risk factors. More than 10% of subjects after age adjustment had at least three risk factors (Figure 1). Of the total 35 diabetic subjects, 5 already had CAD diagnosed previously. The remaining 30 diabetics were asked for consent to perform ETT and CCA-IMT in order to test for new CAD cases. 22 diabetics gave consent for ETT and 19 for CCA-IMT measurements. We also performed CCA-IMT measurements on 27 randomly picked non diabetics.

### Prevalence of CAD risk factors in diabetics and non diabetics

On comparison of CAD risk factors among diabetics and non diabetics (Table 2), the prevalence of hypertension was 31.7% and 15.7% in diabetics Vs non diabetics ( $p = 0.003$ ) respectively. Similarly, the prevalence of high cholesterol ( $\geq 200\text{mg/dL}$ ) and family history of diabetes was 54.3 % ( $p<0.0001$ ) and 77.1% ( $p<0.0001$ ) respectively in diabetics as compare to lower values in non diabetics (Figure 1 and table 2).

We also compared other CAD risk factors between these two groups, however, these comparisons did not reach significance which could be attributable to small sample size or these factors may have an impact independent of diabetes (Table 2).

**Incidence of CAD amongst diabetics and non diabetics:** 22 out of 30 diabetic subjects who did not have CAD on history and previous medical records provided consent for the stress test (Table 3). Based on stress test results, 45% of SAIIn diabetics were positive for CAD diagnosis ( $p<0.001$ , Figure 2, Table 3). Similarly, 63.1% of diabetics and 51.8 % of non diabetics were positive for sub-clinical CAD using CCA-IMT which further stresses the fact that CAD incidence and prevalence is high in SAIIns (Figure 3). To see if there was any correlation of CCA-IMT and CAD, we compared if those who were positive for stress test also had high CCA-IMT. We found that out of 10 subjects that were positive for stress test, 7 were also positive for CCA-IMT ( $p\text{-value} = 0.18$ ) but was not statistically significant. Similarly, we could not find statistical correlation between CAD and diabetes control ( $p\text{-value}=0.56$ ), duration of diabetes ( $p\text{-value}=0.14$ ) and with type of diabetes treatment i.e. with diet ( $p\text{-value}=0.71$ ) and drugs ( $p\text{-value}=0.83$ ) (Data not shown). This could again be attributable to the small sample size.

## Discussion

In this small cohort of 213 South Asian Indian immigrants residing in Georgia, we found higher prevalence of cardiac risk factors in all individuals. Moreover, diabetics had clustering of risk factors as shown by higher prevalence of hypertension, hypercholesterolemia and family history of diabetes mellitus. Subclinical atherosclerosis determined by CCA-IMT was seen in >50% of the entire cohort. A positive ETT suggestive of a high incidence (45%) of asymptomatic CAD was seen in the diabetics.

The high CAD risk factor prevalence rates have consistently been described in countries across the globe: Singapore, Canada, the United Kingdom, South Africa, Trinidad, and the US [25-30]. A population-based study on SAIIs found the prevalence rate of diabetes to be 20% in the US [31]. Studies around the world have shown that from 11% to 20% of all SAIIns and other South Asian groups have diabetes [27]. In our current study, we confirm the presence of diabetes in 16.82 % of the study sample that is higher than any other immigrant as well as general US population [8,31] (Table 1).

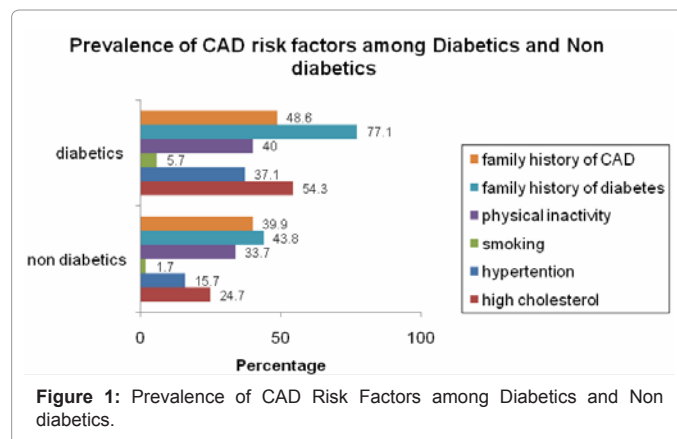


Figure 1: Prevalence of CAD Risk Factors among Diabetics and Non diabetics.

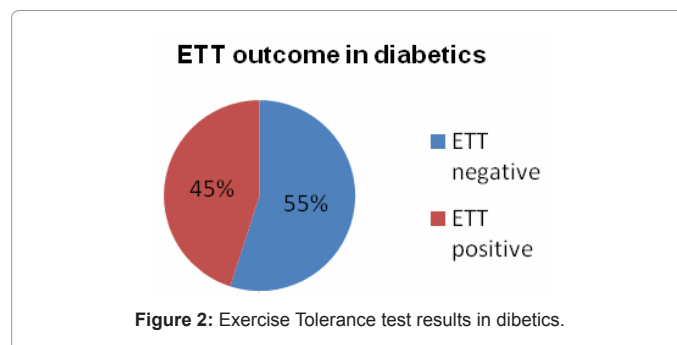


Figure 2: Exercise Tolerance test results in diabetics.

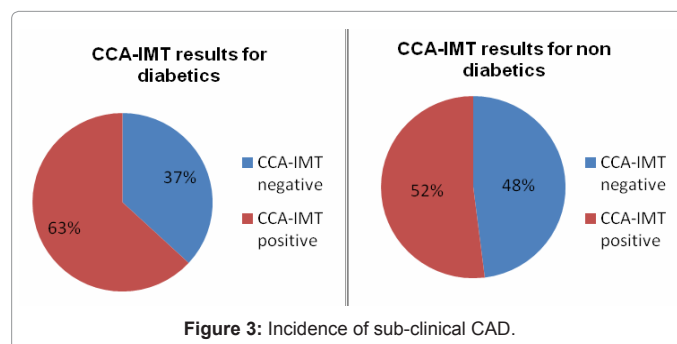


Figure 3: Incidence of sub-clinical CAD.



In the US, South Asian Indian men have more than double the incidence (7% vs. 3%) of myocardial infarction than the general US population [25]. The susceptibility of diabetes amongst South Asians in general and SAIs in particular promotes an adverse CAD risk, even in patients treated for high blood pressure and cardiovascular risk as evident in this study. A population-based study on South Asians found the prevalence rate of diabetes to be 20% in the US [31]. This is higher than the national rates reported by the Centers for Disease Control's.

(CDC's) National Diabetes Surveillance System—in 2004 the diabetes rates were between 4% and 8% for Whites, Blacks, and Hispanics [11]. One study showed that the CAD mortality rate among diabetic SAIs was 3 times higher than that of people with diabetes who were born in England and Wales [4]. The mortality rate difference was greatest in the younger age group, from 30- to 64-year-olds. From our analysis, we found that both the diabetic and non diabetic populations showed high CAD risk factor prevalence with a slight higher figures in diabetics than non diabetics (Table 2) pointing once again towards the belief that SAIs are a high risk population for CAD (Figure 1).

Moreover, other established and emerging risk factors are also under-represented in South Asians than they actually are. Most people that volunteer to participate in such research studies tend to be the ones more proactive about their health, who take better care through diet, exercise and medications. Hence, considering the fact that those who are negligent of their health are also less likely to participate in such research for health assessments; the actual number of people with risk factors would be much higher. Further studies are needed to determine the relative contribution of established and emerging vascular risk factors in SAIs and evaluate clinical outcomes following treatment of these risk factors. Further research is needed to address the pathophysiological mechanism by which diabetes confers an adverse cardiovascular risk in SAIs, and whether there is ethnic variation therein. Studies comparing CAD risk factors amongst Indians living in India to immigrants in Britain [26] highlight that CAD risk factors are markedly higher amongst Indian Punjabi [27] and Gujarati [28] migrants than their counterparts in India. Greater atherogenic effects of diabetes in SAIs might also explain the higher mean levels of CCA-IMT observed in this study, despite their generally better mean levels of risk factors.

Differences in association of diabetes with metabolic syndrome have also been observed between Chinese, Europeans and South Asians, [29] suggesting that SAIs may be uniquely susceptible to the effects of metabolic determinants of CVDs. In a study performed in Canada, levels of CCA-IMT were slightly lower in SAIs as compared to locals of European descent; [30] however, CCA-IMT levels were not adjusted for risk factors and SAIs had a higher prevalence of CVDs than the European counterparts. Inter-observer differences in measurement may also affect estimates of mean differences between populations in CCA-IMT but are unlikely to have substantially influenced the conclusions of the analyses comparing the strengths of associations of risk factors with carotid IMT.

Diabetes mellitus is associated with two-four fold increased risk of CAD and silent ischemia is more common in this group of patients. Detection of silent ischemia by various stress tests has been proposed, but is not recommended due to low prevalence of events and prohibitive cost of screening large diabetic population (DIAD trial). In a large cohort of white men, positive ETT was a strong predictor of cardiovascular death [31]. However, the US Preventive Services Task Force does not endorse exercise stress testing to detect CAD in asymptomatic individuals because of low diagnostic yield (2.7%)

to detect severe coronary artery obstruction that would benefit from revascularization [32]. Exercise thallium scintigraphy was found to be useful in the risk assessment of asymptomatic male siblings of patients with premature CHD [33]. In DIAD trial 22% of the screened subjects had a positive myocardial perfusion scan. On the other hand, our study showed 45% positive ETT among the diabetic subjects. Although our study is limited by a small sample size, it is conceivable that ETT being a less sensitive test must have missed about 20% subjects who would have a positive nuclear scan. On the whole, the entire cohort of SAIs had higher incidence of atherosclerosis as determined by CCA-IMT. These findings suggest that SAI immigrants fall in a higher risk category than other population and it may be reasonable to screen these individuals for asymptomatic CAD.

At the same time, several limitations of this study must be addressed. First, this study had a small sample size as a pilot attempt to explore any possible correlation between CAD and diabetes in SAIs. A larger study will answer these questions before firm recommendations can be made. Second, due to limited funding, only South Asian Indian Hindus are considered in this study to establish a homogenous group. This is in one way to our advantage, since it controls for the differences in diet and lifestyle amongst other religions of South Asia. We plan to include other ethnic groups in a later larger proposal that accounts for subjects from other religious backgrounds. Third, incidence of CAD in non diabetics may not reflect correct numbers as we did not perform stress test in non diabetics and figures are based on history of CAD and available medical health records. Due to its lower sensitivity, ETT may not represent true incidence of CAD. Fourth, due to limited funds, CCA-IMT was also not performed in all diabetics and non diabetics and representative sample of 46 subjects (including both diabetics and non diabetics) was randomly selected from the total sample. Fifth, participants were recruited from local Hindu temples which may not be truly representative of the South Asian community. However, to our knowledge, there is no database available that can provide some census data on SAIs in the US in general and the SAIs in the Southern region of the US. Therefore, SAIs is most readily accessed through their temples of worship. Most SAIs visit temples on weekends. Therefore, our recruitment strategy involved distribution of flyers and announcements that outline the purpose, rationale, and design of the study in main Hindu temples (majority) and other SAI businesses. Moreover, people attending these temples were from mixed ethnic backgrounds; therefore, we anticipate the selection bias is minimal and that the sample is representative of South Asians Indian immigrants living in Georgia.

## Conclusion

Unexpectedly high rates of CVDs in general and CADs in particular in both immigrant and non-immigrant South Asian populations have remained largely unexplained since they were first noted. The susceptibility to diabetes amongst South Asian Indians promotes an adverse CAD risk, as evident by this small study. The key to combating the increasing incidence of CAD among South Asians is early CAD screening and an aggressive treatment of known risk factors and diabetes through both an individual-based as well as a population-based approach aimed at comprehensive risk factor reduction.

Further investigation is needed to assess whether lower thresholds for CAD risk management and early screening for CAD in diabetic South Asians will be beneficial in this population.

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