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Title

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Comparison of Epicardial Adipose Tissue Volume and Coronary Artery Disease Severity in Asymptomatic Adults with versus without Diabetes Mellitus

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Abstract

Epicardial adipose tissue (EAT) has been shown to have important effects on the development of coronary artery disease (CAD) via local paracrine influences on the vascular bed. We compared a cohort of asymptomatic patients with Type II Diabetes (DM) without known CAD to an age and gender matched group of asymptomatic patients without DM from the CTRAD study in which patients underwent a cardiac computed tomography angiogram (CTA), for early detection of CAD. Mean EAT volumes of 118.6 ± 43.0 and 70.0 ± 44.0 cm^3 were found in the DM and non-DM groups respectively. When stratified by presence and severity of CAD, it was found that in the DM (p=0.003) and non-DM groups (p<0.001) there was a statistically significant increase in EAT volume as the patients were found to have increasingly severe CAD. After adjusting for age, race, gender, DM, hypertension, insulin use, BMI, and coronary artery calcium (CAC) score, the presence of >120 cm^3 of EAT was found to be highly correlated with the presence of significant CAD (Adjusted Odds Ratio 4.47, 95% CI (1.35–14.82)). We found that not only is EAT volume an independent predictor of CAD, but that an increasing volume of EAT predicted increasing severity of CAD even after adjustment for CAC score.

Keywords

Coronary Artery Disease; Epicardial Adipose Tissue; Diabetes

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Introduction

Epicardial adipose tissue (EAT) volume has been demonstrated to potentially be a valuable independent predictor of the presence of coronary artery disease (CAD).[1–4] However whether the relationship between EAT volume and CAD persists in asymptomatic patients with and without diabetes mellitus (DM), and if it persists after adjustment for coronary artery calcification (CAC) is unknown. Prior studies investigating this issue have had selection bias, using patients that had indications for cardiovascular imaging, such as anginal symptoms or have used Asian populations, which may have different thresholds for visceral adiposity than other ethnic groups.[5,6] This study was designed to assess the correlation between elevated EAT volume and CAD presence and severity in an ethnically diverse asymptomatic patient population. We assessed this relation using a case control study design, comparing a cohort of asymptomatic patients with and without DM and examined the association of EAT volume with CAD severity adjusted for traditional CAD risk factors, body mass index (BMI) as well as CAC score.

Methods

CT Coronary Angiograms (CTA) were used from the CTRAD study (Cardiac CT's Role in Asymptomatic Patients with DM-II) in which consecutive asymptomatic patients (n=203) with type II DM from three community clinics of the University of California, Irvine, were randomly assigned to either undergo 64-slice CT angiography or continue their usual care. Type II diabetes was defined as a fasting blood glucose of greater than or equal to 126 mg/dL, a physician documented diagnosis of DM, current treatment with oral hypoglycemic medications, current treatment with insulin or treatment with a non-insulin injectable therapy for DM. 92 patients were identified who fell into the DM group. Type I diabetics were not used in this study. These patients were matched 3:1 with age and gender matched non diabetic controls (non-DM) from a CT database of healthy community volunteers that was simultaneously collected to create the total patient population for this case control study.

Exclusion criteria included prior diagnosis of CAD, previous percutaneous coronary transluminal angioplasty (PTCA), previous percutaneous coronary intervention (PCI), coronary bypass grafting (CABG), or the presence or chest pain that was felt to necessitate a cardiac workup. The Institutional Review Board of the University of California approved the study and all study data was handled in accordance with Health Insurance Portability and Accountability Act regulations.

In preparation for image acquisition, patients without contraindications were given oral or intravenous metoprolol tartrate with the goal of reaching a heart rate less than 65 beats per minute. One minute prior to imaging, patients without contraindications were administered sublingual nitroglycerin (0.4 to 0.8mg). Scout images of the thorax were then acquired to define an imaging field that encompassed the entire cardiac volume on a 64-slice Toshiba Aquilion CT system (Toshiba Inc, Tustin, CA). Patients were then intravenously administered 64 to 93mL (mean contrast volume 74.9±3.3mL) of iodinated CT contrast

(Iohexol, Omnipaque, Amersham Health, Cork, Ireland) injected at a rate of 4–5mL/s followed by a 50mL flush of saline through an 18 gauge line.

Using a previously described imaging sequence, routine CT coronary angiography was performed followed by acquisition of a retrospective ECG-gated volumetric data set during a single breath hold.[7] Mean scan time was 9.1 ± 1.4 seconds (Range of 8–13 seconds). Datasets were reconstructed based on a relative-delay strategy at 10% of R-R intervals.

Reconstructed CT datasets were evaluated from a remote workstation (Vitrea 2, Vital Images Inc, Minnetonka, Minnesota) by two independent blinded clinicians who were CTA level III certified. Images were evaluated at several ECG-phases to ensure the highest diagnostic image quality by choosing the optimal data set. Identified atherosclerotic plaques in the epicardial coronary arteries were categorized as either mild to moderate if the observed stenosis was 50–70% or significant if there was a stenosis with greater than 70% luminal obstruction. CAD severity was recorded based on the most severe lesion identified. If no stenosis was present with a 50% or greater luminal obstruction, then the patient was recorded has having no significant disease. CAC scores were calculated by utilizing Vitrea Enterprise Suite (Toshiba Inc, Tustin, CA) and an overall Agagston score was recorded for each patient.[8]

EAT volume was determined by two clinicians who had received dedicated training in measuring EAT and were blinded to the CAD and CAC assessment. Axial non-contrast enhanced images from the mid diastolic phase used for calcium scoring were used to calculate the EAT volume. Tissue was defined as EAT if it was within the parietal pericardial boundary and demonstrated fat density attenuation on CT measured by Hounsfield units (−30 to −190 HU).[9–11] Sequential images from the lower margin of the aortic arch to the inferior cardiac border were used (Range of 35–40 slices per patient). The area of each pocket of epicardial fat was manually traced and a total area of epicardial fat for each slice based on the summation of all pockets was recorded. To achieve a volumetric measurement, the area of epicardial fat was multiplied by the slice thickness (3mm). This volumetric assessment included the epicardial coronary arteries.[12] The volume of EAT as opposed to EAT thickness was used in this study as prior studies using EAT thickness have shown contradictory results, and EAT volume is a more accurate representation of the entire EAT burden.[1]

Categorical variables are presented as percentages and continuous variables are presented as mean values ± standard deviation (SD). All data represented by continuous variables was subjected to a normality analysis which confirmed all data was normally distributed. We evaluated the clinical characteristics of patients with versus those without DM using Chi-squared test for categorical variables and student's T-test for continuous variables. Additionally, we used ANOVA to examine CAD severity stratified into 3 separate categories (none, mild/moderate, significant) versus patient characteristics within the DM and non-DM patient groups. Separately, we used bivariate linear regression to associate EAT volume with previously identified patient characteristics within both the DM and non-DM groups.

Finally, we examined the association between EAT and CAD severity in study participants using several multivariate logistic regression models. A cutoff defined as the presence >120cm^3 of EAT was defined for this analysis. This EAT volume corresponded to 66th percentile of EAT volumes measured in this study. We utilized a sequential modeling technique to assess contribution of additional variables to the model. The first model was adjusted for age, gender, race, diabetes, hypertension, dyslipidemia and the use of insulin therapy. Two additional models were created adjusting for BMI, in addition to the presence smoking. Our fourth model included adjustments for all previously used variables as well as CAC scores. Statistical significance was defined as a p-value less than 0.05. All statistical analysis was performed using SAS 9.3 (SAS Institute, Cary, North Carolina).

Results

Table 1 describes the clinical characteristics of the 362 study patients of which 92 (25.4%) were patients with DM who had no symptoms of coronary artery disease, and 270 asymptomatic patients without DM (non-DM). The mean age in the DM group and non-DM group were 56.2 ± 9.5 and 57.2 ± 9.7 years respectively. In the DM group 57.9% of the patients were female as were 60% of the patients in the non-DM group. The mean body mass index (BMI) for participants with DM and without DM was statistically significantly different (p<0.0001). There was a statistically significant difference in the ethnic makeup of the two groups as well (p<0.0001). Additionally, there was an expected statistically significant difference in medical comorbidities, as those with DM had a higher prevalence of hypertension and dyslipidemia (p<0.0001). Finally, there were more smokers in the non-DM group (p=0.0008).

Among patients in the DM group, 30.4% were identified as having mild to moderate CAD and 27.2% (p<0.001) had significant CAD by CTA (Table 2). Patients in this group who were identified as having CAD were disproportionately older and male compared to those with mild disease. EAT volumes significantly increased with increasing severity of CAD (p=0.003). The presence hypertension, dyslipidemia, insulin therapy, and smoking were not significantly different by severity of CAD in those with DM. Additionally, hemoglobin A1c level and increases in BMI did not significantly change with the severity of CAD.

Patients without DM had a similar burden of mild/moderate CAD (29.6%) to the DM group, but they had a much lower incidence of significant CAD at 5.2%. Non-DM patients also demonstrated a statistically significant association of increasing age with increasing severity of CAD along with a male predominance. Those without DM also showed a clear relationship of CAD severity with the presence of the traditional risk factors hypertension, dyslipidemia and smoking.

Mean EAT volumes for DM and non-DM patients respectively can be seen in Table 3. Figure 1 illustrates the EAT distribution in both groups. Among non-DM patients, but not DM patients, age >60 years and hypertension were found to be significantly associated with an increased mean EAT volume. Male subjects in both groups had an increased EAT volume as well. EAT volume was found to be significantly increased as BMI and CAC increased in both DM and non-DM patient groups, except in those with DM and with BMI

40, the EAT volume was slightly lower than in those with BMI 30–39.9 (Table 3). There was a direct relationship between increasing EAT volume and worsening severity of CAD for both patients with and without DM (p=.003 and p=.0001, respectively).

We assessed sequential multivariate logistic regression models to test the associating EAT of > 120 cm^3 with the presence of significant CAD. After adjustments for age, gender, race, diabetes, hypertension, dyslipidemia and insulin therapy, patients with EAT> 120 cm^3 were significantly more likely to have significant CAD (OR = 6.04, p=0.0006). This increased likelihood for presence of CAD persisted with the addition of adjustment for BMI (OR = 6.12, p=0.001), as well as the addition of smoking (OR = 5.40, p=0.002). After additional adjustment for CAC score, patients with a EAT>120 cm^3 continued to have an increased odds (OR of 4.47, p=0.01) for the presence of significant CAD. Finally, we also adjusted for the interaction between diabetes and Hispanic race in all 4 models from the multivariate analyses (Table 4), and the interaction terms were not significant in all 4 models (p values of 0.98, 0.76, 0.74, 0.82).

Discussion

CAD and its complications continue to be the leading cause of the death in the United States, and in many countries abroad.[13] With the obesity epidemic, consequent insulin resistance and the increased prevalence of type II DM, death from CAD will remain high for the foreseeable future. Traditional markers of obesity including BMI rely on the global burden of body obesity, including less metabolically active subcutaneous generalized depots of adipose. There is a non-linear association of BMI and CAD, however visceral adiposity has shown a more linear relationship with insulin resistance, suggesting that global fat, as reflected by BMI, may be an inaccurate and limited surrogate of attendant cardiovascular disease risk.[12] Studies have suggested that central obesity, a measure of visceral obesity, is a more precise measure of cardiovascular risk.[14,15]

EAT is defined as adipose or fat tissue within the parietal pericardium and is one of the local depots of visceral adipose tissue.[16] Due to its close anatomical relationship with the epicardial coronary circulation and its unique tissue properties, EAT may play an intimate role in the development and progression of CAD.[17,18] Prior studies have shown that EAT is a source of inflammatory mediators which may contribute to the development of CAD or at the very least be highly correlated with the concurrent presence of CAD.[19–21] The perivascular location of EAT, allowing a potential paracrine effect on epicardial coronary arteries, and its correlation with other forms of visceral adiposity, a known cardiovascular risk factor, make it a unique and promising marker.[19–21] Using echocardiography, cardiac magnetic resonance imaging (CMR) and computed tomography (CT) a clear association has been seen between EAT volume and CAD independent of traditional risk factors for CAD.[14,22,23] Recent work has also demonstrated a correlation between EAT volume and increasing values of the CAC score.

We found a robust relationship between increasing EAT volume and significant CAD after adjusting for BMI and CAC score. To our knowledge there has not been a study illustrating the independence of EAT from CAC score. Increasing EAT volume had a linear relationship

with worsening severity of CAD, in those with and without diabetes. Those with diabetes had much higher absolute volumes of EAT compared to those without diabetes, however in each group increasing EAT volumes were associated with greater severity of CAD.

Unlike EAT, we found that BMI did not have a linear relationship with increasing severity of CAD in those with DM or those without DM. This finding corroborates the results of other studies that have shown the limitations of BMI, particularly in patients with DM where BMI has repeatedly been shown to have highly non-linear relationship with CAD.[24,25] Visceral adiposity as measured by EAT may be a good surrogate maker of true or visceral obesity, as compared to conventional markers of adiposity, including BMI.

By being accessible for measurement by echocardiography, CT and magnetic resonance imaging (MRI), EAT can be calculated from numerous imaging modalities and thus has a robust clinical use potential.[23,26] This potential goes beyond measurements such as CAC which are confined solely to a single imaging modality. A patient having a scan that encompassed their cardiac silhouette could have their EAT volume calculated even if that imaging study was intended for alternate purposes as in the case of a CT pulmonary angiogram or thoracic MRI. Additionally, millions of echocardiograms are performed on patients yearly, making this measurement of visceral adiposity even more readily available and valuable.

Prognostic indicators such as CAC have been shown to be surrogate markers of the presence of CAD, but have limitations and have not been widely adopted in clinical practice.[27–29] Coronary CTA is a useful predictor of the presence and to some degree the severity of CAD, but requires iodinated contrast and an increased dose of radiation when compared to non-contrast studies and for these and other reasons is not widely used in clinical practice.[30]

An additional finding of significance in this study was the lack of predictive value of traditional risk factors in the DM group. Hypertension, dyslipidemia and smoking were not significantly associated with the presence or severity of CAD. This finding was not consistent with the non-DM group where these risk factors did show a significant association with CAD. The reason for this may be due to DM in and of itself being a CAD risk equivalent and perhaps attenuating the association of hypertension and dyslipidemia with CAD. Finally, our study population of asymptomatic patients was majority Hispanic. Previous work assessing the relationship between EAT and CAD in asymptomatic cohorts have not utilized a multi-ethnic sample and therefore are not widely applicable to the heterogeneous population of the United States.[3,22]

Limitations of our study include the fact that it a statistically significant difference exists in the ethnic breakdown of the DM and non-DM groups, however our analysis did adjust for ethnicity. Our confidence intervals were wide due to a smaller sample size, however the associations we found were robust. Finally, our analyses were cross-sectional and therefore we can only report on associations and cannot comment on causation.

This study is the first study to our knowledge to illustrate that volumetric EAT measurements can be used to predict the presence and severity of CAD in asymptomatic patients with and without DM after adjustment of CAC. Future studies could ascertain the

clinical utility of routinely assessing EAT and show the longitudinal prognostic value of this measure.

Acknowledgments

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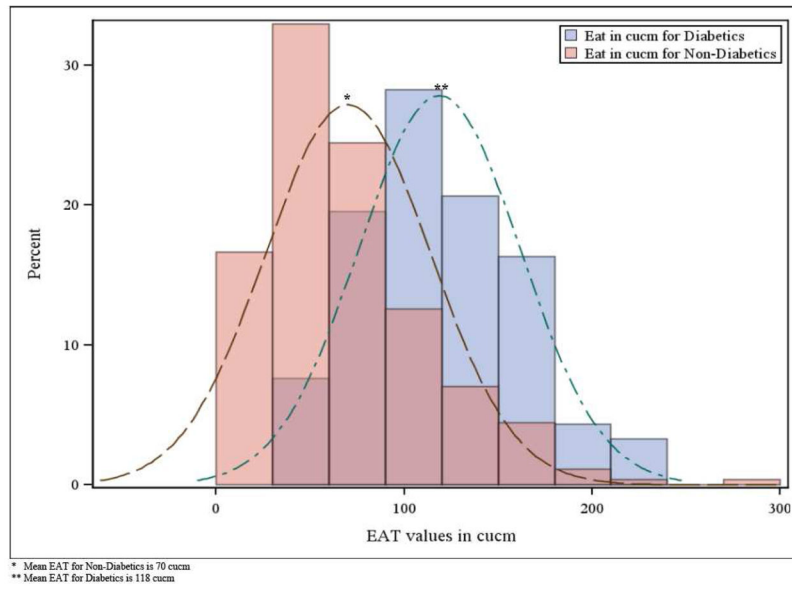
Figure 1. Epicardial Adipose Tissue Distribution in subjects with Type II DM and Controls (Non-Diabetics)
Represented here is a graph of the distribution of epicardial adipose tissue (EAT) volumes in the two patient populations. The diabetic group is blue and the non-diabetic groups is represented in beach, the crossover between the groups is represented in purple.

Table 1

Characteristics of Study Participants

	Type II Diabetes Mellitus		
	Yes n=92	No n=270	p-value
Men	39 (42.4%)	108 (40.0%)	0.39
Women	53 (57.6%)	162 (60.0%)	0.69
White	17 (18.5%)	197 (73%)	
Hispanic	63 (68.5%)	11 (4.1%)	<0.0001
Asian	9 (9.8%)	49 (18.2%)	
Other Race	3 (3.3%)	13 (4.8%)	
EAT[†] Continuous (cm^3) ± SD	118.6 ± 43.0	70.0 ± 44.0	<0.0001
BMI[‡] Continuous (kg/m^2) ± SD	31.9 ± 7.5	26.8 ± 5.1	<0.0001
BMI (kg/m^2)			
<25	14 (15.2%)	111 (41.1%)	
25 – 29.9	25 (27.2%)	96 (35.6%)	<0.0001
30 – 39.9	43 (46.7%)	57 (21.1%)	
40	10 (10.9%)	6 (2.2%)	
Hypertension[*]	69 (75.0%)	107 (39.6%)	<0.0001
Dyslipidemia[§]	54 (58.7%)	92 (34.1%)	<0.0001
Insulin Therapy	19 (20.6%)	0 (0%)	n/a
Smokers	9 (9.8%)	72 (26.7%)	0.0008

[†]EAT = Epicardial Adipose Tissue Volume

[‡]BMI = Body Mass Index

[*]Defined as treatment with any antihypertensive medication

[§]Defined as treatment with Statin therapy

Table 2

Relationship between Clinical Characteristics of the Study Participants and Coronary Artery Disease Severity

	Type II DM CAD Severity				Non-DM CAD Severity			
	None	Mild to Moderate	Significant	p-value	None	Mild to Moderate	Significant	p-value
Number of Patients	39 (42.4%)	28 (30.4%)	25 (27.2%)	<0.001	181 (67.0%)	80 (29.6%)	8 (3.0%)	<0.001
Age (years)	50.6 ± 6.9	59.0 ± 8.5	62.0 ± 9.4	<0.001	54.5 ± 8.4	62.5 ± 9.94	64.0 ± 9.0	<0.001
Men	7 (18.0%)	14 (50.0%)	18 (72.0%)	<0.001	57 (31.5)	43 (53.8)	7 (87.5)	<0.001
Women	32 (82.0%)	14 (50.0%)	7 (28.0%)	<0.001	124 (68.5)	37 (46.3)	1 (12.5)	<0.001
White	5 (12.8%)	4 (14.3%)	8 (32.0%)		131 (72.4)	58 (72.5)	7 (87.5)	0.66
Hispanic	32 (82.0%)	21 (75.0%)	10 (40.0%)	0.02	10 (5.5)	1 (1.3)	0 (0)	
Asian	1 (2.6%)	2 (7.1%)	6 (24.0%)		31 (17.1)	17 (21.3)	1 (12.5)	
Other Race	1 (2.6%)	1 (3.6%)	1 (4.0%)		9 (5.0)	4 (5.0)	0 (0)	
EAT Continuous (cm^3) ± SD	107.05 ± 39.4	112.7 ± 37.2	143.1 ± 46.0	0.003	63.5 ± 40.0	79.5 ± 48.6	120.0 ± 40.7	<0.001
Hemoglobin A1c (%)	8.01 ± 1.68	8.15 ± 1.83	7.57 ± 1.45	0.42	n/a	n/a	n/a	n/a
BMI Continuous (kg/m^2) ± SD	32.7 ± 9.0	31.6 ± 4.9	31.1 ± 7.6	0.7	26.8 ± 5.1	26.3 ± 5.0	30.0 ± 6.2	0.05
BMI (kg/m^2)								
<25	6 (15.4%)	2 (7.1%)	6 (24.0%)	0.25	77 (42.5)	32 (40.0)	2 (25.0)	0.12
25 − 29.9	11 (28.2%)	9 (32.1%)	5 (20.0%)		62 (34.2)	32 (40.0)	1 (12.5)	
30 − 39.9	15 (38.5%)	16 (57.1%)	12 (48.0%)		39 (21.5)	14 (17.5)	4 (50.0)	
40	7 (18.0%)	1 (3.6%)	2 (8.0%)		3 (1.7)	2 (2.5)	1 (12.5)	
Hypertension	26 (66.7%)	21 (75.0%)	22 (88.0%)	0.16	60 (33.1)	40 (50.0)	6 (75.0)	0.004
Dyslipidemia	21 (53.8%)	17 (60.7%)	16 (64.0%)	0.7	46 (25.4)	41 (51.3)	5 (62.5)	<0.001
Insulin Therapy	10 (25.6%)	3 (10.7%)	6 (24.0%)	0.29	0 (0.0)	0 (0.0)	0 (0.0)	n/a
Smokers	5 (12.8%)	1 (3.6%)	3 (12.0%)	0.41	39 (21.5)	26 (32.5)	7 (87.5)	<0.001

Chi-Squared Test of Independence was used for categorical variables and ANOVA for continuous variables

Table 3

Relationship between Patient Characteristics and Mean EAT

| | Type II Diabetes Mellitus | | | |
| | Yes | | No | |
	EAT Volume (cm^3)	p-value	EAT Volume (cm^3)	p-value
Overall	118.3 ± 42.2		70.0 ± 44.0	
Men	130.3 ± 48.5	0.02	78.1 ± 48.7	0.02
Women	109.9 ± 36.6		64.5 ± 39.8	
Age (years)				
35–60	112.2 ± 42.7	0.05	63.4 ± 41.9	0.0003
>60	131.1 ± 41.5		85.0 ± 45.2	
White	136.1 ± 37.6	0.03	68.6 ± 45.9	0.43
Asian	113.8 ± 42.6		73.4 ± 32.1	
Hispanic	135.0 ± 43.9		78.0 ± 42.2	
Other Race	69.4 ± 29.5		58.7 ± 25.6	
BMI (kg/m^2)				
<25	97.6 ± 38.0	0.01	55.0 ± 37.6	<0.0001
25 – 29.9	103.6 ± 37.5		76.5 ± 41.1	
30 – 39.9	131.6 ± 44.6		82.4 ± 43.9	
40	129.2 ± 36.5		125.8 ± 89.7	
Hypertension	121.5 ± 43.05	0.26	80.6 ± 47.7	0.001
Dyslipidemia	116.3 ± 37.7	0.54	78.3 ± 47.0	0.06
Smokers	130.7 ± 44.1	0.4	78.3 ± 47.0	0.06
Insulin Therapy	114.3 ± 52.0	0.63	n/a	n/a
Calcium Score				
Zero	106.6 ± 38.4	0.03	62.6 ± 39.7	0.003
1–100	121.1 ± 47.1		71.0 ± 41.8	
101–400	118.9 ± 38.9		78.6 ± 50.1	
>400	141.3 ± 42.5		92.6 ± 51.5	
CAD Severity				

| Type II Diabetes Mellitus | | | | |
| | Yes | | No | |
	EAT Volume (cm^3)	p-value	EAT Volume (cm^3)	p-value
None	107.0 ± 39.4	0.003	63.5 ± 40.0	0.0001
Mild to Moderate	112.7 ± 37.2		79.5 ± 48.6	
Significant	143.1 ± 46.0		120.0 ± 40.7	

Values are expressed as mean ± standard deviation

Epicardial Adipose Tissue (EAT)/Pericardial Fat defined as fat density (Attenuation values between −30 to −190 HU) observed within the parietal pericardium boundary.

Body Mass Index (BMI), Coronary Artery Disease (CAD)

Table 4

Multivariate Logistic Regression Models: Association of EAT (>120 cm^3) with the presence of Coronary Artery Disease

Adjustors	Odds Ratio (95% Confidence Interval)	p-value
Age, Gender, Race, DM, Hypertension [*], Dyslipidemia [†] and Insulin Therapy	6.04 (2.17–16.78)	0.0006
Age, Gender, Race, DM, Hypertension, Dyslipidemia, Insulin Therapy and BMI	6.12 (2.02–18.51)	0.001
Age, Gender, Race, DM, Hypertension, Dyslipidemia, Insulin Therapy, BMI and Smoking	5.40 (1.81–16.09)	0.002
Age, Gender, Race, DM, Hypertension, Dyslipidemia, Insulin Therapy, BMI, Smoking and Calcium Score[‡]	4.47 (1.35–14.82)	0.01

[*] Defined as treatment with any antihypertensive medication

[†] Defined as treatment with Statin therapy

[‡] Calcium Score categories defined as 99 and >100

Epicardial Adipose Tissue (EAT)/Pericardial Fat defined as fat density (Attenuation values between −30 to −190 HU) observed within the parietal pericardium boundary.

Body Mass Index (BMI)