

Study of Epicardial Adipose Tissue Thickness and Adiponectin Level to Predict Coronary Artery Disease in Egyptian Patients

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Abstract: Background: nowadays, the echocardiographic assessment of EATT is gaining high interest since it is safe, non-invasive and reproducible. There is a growing evidence supports the role of EAT in the pathogenesis of CAD through local release of inflammatory cytokines. Our aim was to study the interrelationship between EATT & serum level of adiponectin and their utilization in predicting CAD in Egyptian patients. **Methods:** we enrolled 50 patients who underwent coronary arteries angiography for suspected CAD, and accordingly they were divided equally into 25 patients with CAD and 25 ones without CAD. EATT from the right ventricular free wall in the parasternal long-axis view was measured by 2D transthoracic echocardiography. Coronary angiographies were analyzed for the presence and severity of CAD. Serum adiponectin, lipid profile and glucose homeostasis parameters were measured. **Results:** A highly significant increased EATT was found in CAD patients compared to control group (8.49 ± 3 mm vs. 4.97 ± 3.3 mm; $t = 3.95$, $p = 0.0003$) with An EATT of > 3.7 mm predicted the presence of CAD with sensitivity of 88 %, specificity of 72 %, PPV of 75.86 % and a NPV of 85.71 %. It was increased with severity of CAD (multivessels 12.2 ± 1.43 mm vs. 5.18 ± 1.54 mm; $p < 0.0001$). Multiple logistic regression analysis for the prediction of significant CAD risk factors revealed EATT to be an Independent Risk Factor for CAD (OR = 1.329, $p = 0.005$). Also it was positively correlated to the following risk factors of CAD; hypertension, positive family history of CAD, anthropometric measurements, all glucose homeostasis parameters, TC, TG, LDL-C, degree of coronary arteries stenosis and severity of vessels affected. There was significant negative correlation between EATT and both serum adiponectin level as well as HDL-C. Furthermore, Serum adiponectin level was found very significantly low in CAD patients compared to control group (4.06 ± 2.8 μ g/ml vs. 7.7 ± 2.8 μ g/ml; $t = 3.59$, $p = < 0.0001$) with an adiponectin serum concentration of < 6.3 μ g/ml predicted the presence of CAD with sensitivity of 68 %, specificity of 64 %, PPV of 65.38 % and a NPV of 66.67 %. It was in a significant negative correlation with the following risk factors of CAD; hypertension, positive family history of CAD, anthropometric measurements, all glucose homeostasis parameters, TC, TG, LDL-C, degree of coronary arteries stenosis, severity of vessels affected, while in a positive correlation with HDL-C. **Conclusions:** Epicardial adipose tissue thickness measured by transthoracic echocardiography was significantly associated with the presence and severity of CAD and correlated with a diponectin level in Egyptian patients.

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Abbreviations: **2D:** 2 dimensions, **BMI:** Body mass index, **WC:** waist circumference **CAD:** Coronary artery disease, **EAT:** Epicardial adipose tissue, **EATT:** Epicardial adipose tissue thickness, **FBG:** fasting blood glucose, **2h PP:** 2 hours post prandial **HbA1C:** hemoglobin A1C, **TC:** total cholesterol, **TG:** triglycerides, **HDL-C:** high density lipoprotein cholesterol, **LDL-C:** low density lipoprotein cholesterol, **PPV:** positive predictive value **NPV:** negative predictive value, **OR:** odds ratio, **ROC:** receiver operating characteristics.

1. Introduction

Although a high body mass index is related to the development of cardiovascular risk factors, there are numerous evidences supporting the idea that the regional fat accumulation, its function and its endocrine products are more important than the excess of total body adiposity per se when considering the risk of cardiovascular disease development [1]. Among visceral adipose tissues, growing evidences suggest

that excessive accumulation of cardiac adiposity within the pericardial sac particularly epicardial coronary vessels, has been suggested to play an important role in the development of atherosclerosis because of its proximity to myocardium and absence of fascia, epicardial fat may directly affect the coronary artery and myocardium through paracrine secretion of anti and pro-inflammatory adipokines, contributing to development of CAD (2) (3).

Adipokines are cytokines mainly produced by adipose tissue that have a role in the regulation of other cytokines and in the metabolism of glucose- insulin and lipids (4). Adiponectin levels are lower in obese individuals and in those with increased cardiovascular risk and are inversely associated with deposits of abdominal visceral, epicardial and intrathoracic fat [5].

Echocardiographic assessment of epicardial fat may be a helpful tool not only for diagnostic purposes, as marker of visceral adiposity and inflammation, but also for therapeutic interventions with drugs that can modulate the adipose tissue [2].

EAT locally express adiponectin protein, with significantly lower levels in patients with CAD [6].

Although several studies have been done to investigate the role of either adiponectin or EATT in CAD, few clinical studies investigated the combined role of EATT and serum adiponectin levels with regard to their association with CAD especially in the developing countries. Thus, the present study was to evaluate whether a relationship exist between EATT measured by echocardiography and serum adiponectin with CAD in Egyptian patients.

2. Patients and methods

Patients: After departmental ethical committee approval and all participants written consent were obtained, 50 patients who underwent elective coronary angiography for the evaluation of suspected CAD were included in this study over a period 10/ 2015 to 6 / 2016. All subjects were selected from Internal Medicine and Cardiology Outpatient Clinics of Sayed Galal University Hospital.

The diagnosis and severity assessment of CAD were made by coronary angiography. Patients with mild (<50 % luminal narrowing) were excluded and those with moderate to severe CAD (>50 % luminal narrowing) were included in the study as patients group. Patients were excluded if they had any of the following: chronic renal and or hepatic disease, history of prior coronary revascularization, patients with pericardial effusion, and whose transthoracic echocardiographic view was inadequate for the measurement of epicardial adipose tissue thickness.

Methods:

All participants were subjected to:

(1) Full history: with special emphasis on risk factors as: diabetes mellitus, hypertension, dyslipidemia, cigarette smoking and family history of CAD. Diabetes mellitus was defined according to ADA as a fasting plasma glucose ≥ 126 mg/dl or current medications either oral or insulin therapy. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg and /or a diastolic blood pressure ≥ 90 mmHg or current antihypertensive treatment. Dyslipidemia was defined as a TC ≥ 200 mg/dl, TG ≥ 150 mg/dl, LDL-C ≥ 130

mg/dl, HDL-C < 40 mg/dl in men and < 50 mg/dl in women or current lipid modifying agent treatment. Smoking was classified as current smoking if the patient smoked or quit within the last 30 days and not smoking if the patients never smoked or smoked in the remote past. Positive family history if one or more of 1st degree relative sustained any CAD events. BMI was calculated as the weight in Kilograms divided by the squared height in meters (kg/m^2). WC was measured at the end of expiration between the midpoint of the last rib and superior iliac crest, in centimeters, using a non-elastic tape measure. Central obesity was considered if the WC was ≥ 90 cm in men and ≥ 80 cm in women. WHO cut-off for BMI ($30 \geq \text{kg}/\text{m}^2$ was considered obese) was used [7]. Blood pressure was measured using a mercury manometer. Both SBP & DBP were measured from each arm of each participant following a minimum rest of 20 minutes.

(2) Laboratory investigations: All biochemical tests were done by OLYMPUS 7500 AU 2700 ANALYSER, at baseline, in the morning after an overnight fast 12 - 14 hours; 5 ml of venous blood samples were taken from each subject participating in the study and each was put into plain tube and was left to clot and the serum was separated by centrifugation for 15 minutes at 3000xg. The separated serum was stored at -20°C for the measurement of:

(a) Fasting blood glucose (FPG): glucose oxidase based assay was used. Another 5 ml of venous blood samples were taken 2-hours after meal for 2h PP level. The test was repeated twice and average values were recorded. ADA criteria for diagnosis of DM and pre-DM status were used [8].

(b) HbA1C: by using National Glycohemoglobin Standardization program (NGSP)-certified method and standardized to Diabetes Control and Complication Trial (DCCT) In diabetic patients value A1C ≥ 6.5 % [9].

(c) Lipid profile including: TC, HDL-C and TG levels were measured with standard enzymatic spectrophotometric technique. Provided plasma TG concentrations are < 400 mg/dl, plasma low density lipoprotein-cholesterol (LDL-C) was calculated from the equation of Friedwald *et al.*, [10] $\text{LDL-C (mg/dl)} = \text{TC (mg/dl)} - \text{HDL-C (mg/dl)} - \text{TG}/5$.

(d) Renal and liver function tests: including blood urea, serum creatinine, ALT and albumin were evaluated by colorimetric method Kinetic UV test.

(e) Serum Adionectin Levels: were measured using the RD 195023100 human Adiponectin ELISA Kit (Biovender, Heidelberg, Germany) for the quantitative measurement of human adiponectin in serum. The limit of detection for adiponectin assay was 0, 47 $\mu\text{g}/\text{ml}$ [11].

(3) Echocardiographic Study

Echocardiographic examination was performed

using a Philips (USA) Cardiac ultrasound machine transducer with a 3.5 MHZ by an echocardiographer blinded to clinical and coronary angiography data. All measurements were done according to the American Society of Echocardiography [12]. The EATT was identified as the echo-free space between the outer wall of myocardium and the visceral layer of pericardium and its thickness was measured from standard parasternal long axis view on the free wall of the right ventricle at end-systole in three cardiac cycles, using the aortic annulus as an anatomical landmark. The thickest point of the EAT was measured in each of three cycles, and the average value was calculated. Epicardial fat thickness is best measured at end-systole, because it is compressed during diastole [13].



Fig. 1: Echocardiograph shows the mediastinal fat (above) and the epicardial fat (below)

(4) Coronary angiography

In a fasting state, elective coronary angiography was performed by two experienced invasive cardiologist using Judkins method, following the percutaneous puncturing of the femoral artery approach. Multiple views were obtained in all coronary arteries, including left circumflex coronary artery (LCX), left anterior descending (LAD) and Right coronary artery (RCA) in at least 3 views. Patients were classified as positive CAD defined as > 50 % stenosis in at least one major coronary artery, or negative CAD with no angiographic evidence of significant coronary artery occlusion. Severity of CAD were classified according to number of stenosis of major coronary artery LAD, RCA, and LCX as single, two and three vessels disease. Coronary angiography was recorded in Digital Imaging and Communication in Medicine format.

(5) Statistical analysis of the results: [14]

The collected data were revised, organized, tabulated and statistically analyzed using statistical package for social sciences (SPSS) version 23.0 for

windows. Descriptive results were expressed as **mean ± standard deviation (SD)** or number (percentage) of patients with CAD. **Student t-test:** For statistical significance between 2 groups by (P-value) as $p < 0.05$ significant. **χ^2 -test** (Chi-square test) for statistical significant relation between different variables and grades in qualitative data (or **percentage**) **ANOVA** or **F-test:** For significant difference between more than 2 means. **Pearson correlation** was used to study the relationship between variables. **Uni-variate logistic regression** was first used to quantify the association between all variables and the presence of CAD, followed by a **multiple logistic regression** to identify the independent predictors – risk factors – for the presence of CAD with calculation of **Odds ratios** and 95% confidence intervals.

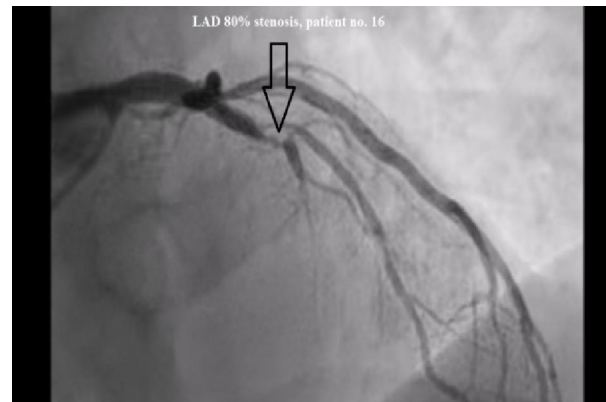


Fig. 2: shows the coronary angiography obtained from patient no.16 demonstrating 80% stenosis of LAD.

3. Results

The baseline Clinical, biochemical and radiological characteristics of all 50 patients enrolled in our study are summarized in **table (1)**; In the CAD group (25 patients), the ages ranged from 44 to 66 years with mean age of 57.28 ± 5.67 years; 11 were males (44%) and 14 were females (56%), while in the control group (25 subjects) the ages ranged from 43 to 66 years with mean age of 56.64 ± 6.08 years; 10 were males (40%) and 15 were females (60%) with insignificant statistical difference between ages and sexes in both groups ($t = 0.38$ & 0.30 , $p = 0.702$ & 0.774 respectively).

In the group of patients with CAD, 16 patients out of 25 (64%) were by history diabetic while the remaining 9 (36 %) were not, 19 (76 %) patients out of 25 were by history hypertensive while the remaining 6 (24 %) were not, all of the 25 (100 %) were dyslipidemic, 10 patients (40 %) were smoker while the remaining 15 (60 %) were not, 18 patients out of 25 (72 %) had a positive family history for CAD while the remaining 8 (28 %) did not.

In the group of patients without CAD, 13 patients out of 25 (52 %) were by history diabetic while the remaining 12 (48 %) were not, 4 patients out of 25 (16%) were by history hypertensive while the remaining 21 (84 %) were not, 17 patients out of the 25 (68 %) were dyslipidemic while the remaining 8 (36 %) were not, 7 patients (28 %) were smoker / and or had cigarette smoking history while the remaining 18 (72 %) were not, 12 patients out of 25 (48 %) had a positive family history for CAD while the remaining 13(52 %) did not.

There was a high statistical significance between CAD and non CAD groups regarding all of the following variables; history of hypertension, systolic, diastolic blood pressures, TC and HDL-C [(t = 15.781 & p = 0.0001), (t = 4.4 & p < 0.001), (t = 4.5 & p = 0.000), (t = 4.20 & p = 0.000) & (t = 3.37 & p < 0.001)] respectively, while only a significant statistical difference were shown between the 2 studied groups regarding the following variables; history of

dyslipidemia, serum TG and serum LDL-C levels [(t = 7.292 & p = 0.004), (t = 2.37 & p = 0.02) & (t = 2.59 & p = 0.01)] respectively.

There was no statistical difference in between the 2 studied groups regarding all of the following variables; history of diabetes, obesity, history of smoking, positive family history, weight, height, body mass index, WC, FBG, 2h pp and HbA1C % [(t = 0.33 & p = 0.567), (t = 0.01 & p = 0.753), (t = 0.36 & p = 0.551), (t = 2.08 & p = 0.149), (t = 1.59 & p = 0.057), (t = 0.12 & p = 0.90), (t = 1.69 & p = 0.09), (t = 1.03 & p = 0.088), (t = 0.80 & p = 0.42), (t = 1.43 & p = 0.15) & (t = 1.37 & 0.17)] respectively.

A highly significant increased EATT was found in CAD patients compared to control group (8.49±3mm vs. 4.97±3.3 mm; t = 3.95, p = 0.0003).

Furthermore, Serum adiponectin level was found very significantly low in CAD patients (4.06 ± 2.8 µg/ml vs. 7.7± 2.8 µg/ml; t = 3.95, p < 0.0001) (Fig. 3).

Table (1): shows the baseline clinical, biochemical and Echocardiographic characteristics of the 2 studied groups with the statistical differences between them:

Studied parameter		Patients (n=25)	Control (n=25)	(t)	(p)	Sig.
Age (years)	Mean ± SD	57.28 ± 5.67	6.08 ± 56.64	0.38	0.702	NS
Sex	Male	11 (44%)	10 (40%)	0.30	0.774	NS
	female	14 (56%)	15 (60%)			
diabetes	+ve	16 (64%)	13(52%)	0.33	0.567	NS
	-ve	9 (36%)	12 (48%)			
hypertension	+ve	19 (76%)	4 (16%)	15.781	0.0001	HS
	-ve	6 (24%)	21 (84%)			
dyslipidemia	+ve	25 (100%)	17 (68%)	7.292	0.004	S
	-ve	0 (0%)	8 (32%)			
obesity	+ve	17 (68%)	9 (36%)	0.01	0.753	NS
	-ve	8 (32%)	16 (64%)			
smoking	+ve	10 (40%)	7 (28%)	0.36	0.551	NS
	-ve	15 (60%)	18 (72%)			
+ve family history	+ve	18 (72%)	12 (48%)	2.08	0.149	NS
	-ve	7 (28%)	13 (52%)			
Weight (KG)	Mean ± SD	95.60±13.59	86.68 ±18.34	1.59	0.057	NS
Height (m)	Mean ± SD	1.704±0.08	1.707±0.079	0.12	0.90	NS
BMI (Kg/M ²)	Mean ± SD	32.64±6.35	29.44±6.97	1.69	0.09	NS
WC (cm)	Mean ± SD	103.72±12.34	100.84±10.34	1.03	0.088	NS
SBP (mmHg)	Mean ± SD	148.4 ± 19	118 ± 27	4.4	< 0.001	HS
DBP (mmHg)	Mean ± SD	89 ± 10	77.6 ± 7.2	4.5	0.000	HS
FBG (mg/dl)	Mean ± SD	149.3±42.9	138.8 ± 48.8	0.80	0.42	NS
2h PP (mg/dl)	Mean ± SD	243.6±74.6	207.9 ±99	1.43	0.15	NS
HbA1C%	Mean ± SD	6.92 ± 0.81	6.59± 0.89	1.37	0.17	NS
TC (mg/dl)	Mean ± SD	242.2±52.1	148.6 ±70.2	4.20	0.000	HS
TG (mg/dl)	Mean ± SD	158.1 ± 28.3	114.0 ±42.1	2.37	0.02	S
HDL-c (mg/dL)	Mean ± SD	38.3 ± 14.3	60.9 ± 19.9	3.37	< 0.001	HS
LDL-c(mg/dL)	Mean ± SD	122.2 ± 15.9	92.8 ± 31.8	2.59	0.01	S
S.Adiponectin (µg/dl)	Mean ± SD	4.06 ± 2.8	7.7± 2.8	4.596	< 0.0001	HS
EATT (mm)	Mean ± SD	8.49 ± 3.0	4.97± 3.3	3.95	0.0003	HS

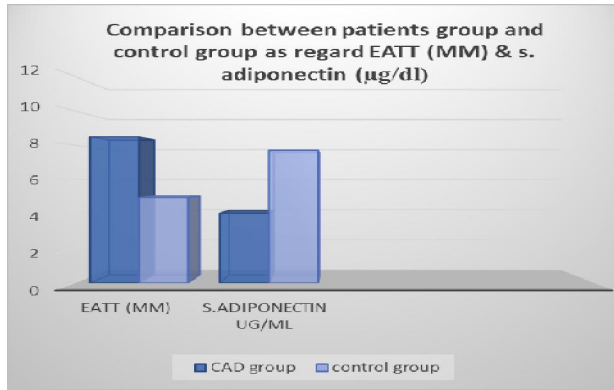


Fig 3: comparison between CAD and non-CAD groups regarding EATT & s. Adiponectin

Correlation between both serum adiponectin level & EATT with various clinical, biochemical, echocardiographic and angiographic variables in the 2 studied groups.

Serum adiponectin was found to be in a significant negative correlation with the presence of hypertension ($r = -0.27$ & $p = 0.04$), positive family history of CAD ($r = -0.28$ & $p = 0.04$), BMI ($r = -0.54$ & $p = 0.03$), WC ($r = -0.51$ & $p = 0.04$), FBG ($r = -0.44$ & $p = 0.02$), 2hpp ($r = -0.64$ & $p = 0.03$), HbA1C

($r = -0.71$ & $p = 0.02$), TC ($r = -0.71$ & $p = 0.03$), LDL-C ($r = -0.42$ & $p = 0.04$), TG ($r = -0.45$ & $p = 0.04$), EATT ($r = -0.58$ & $p = 0.03$) and in a significant positive correlation with HDL-C ($r=0.12$ & $p=0.04$) however, no significant correlation was found between serum adiponectin level and the following variables; age ($r = 0.04$ & $p = 0.77$), male sex ($r = 0.01$ & $p = 0.97$), female sex ($r = -0.01$ & $p = 0.96$) and history of smoking ($r = -0.05$ & $p = 0.74$). (**Table 2**).

EATT was found to be in a significant positive correlation with the presence of hypertension ($r = 0.36$ & $p = 0.01$), positive family history of CAD ($r = 0.036$ & $p = 0.01$), BMI ($r = 0.51$ & $p = 0.04$), WC ($r = 0.61$ & $p = 0.02$), FBS ($r = 0.41$ & $p = 0.04$), 2hpp ($r = 0.521$ & $p = 0.04$), HbA1c% ($r = 0.37$ & $p = 0.04$), TC ($r = 0.45$ & $p = 0.04$), LDL-C ($r = 0.51$ & $p = 0.04$), TG ($r = 0.49$ & $p = 0.04$) and in a significant negative correlation with HDL-C ($r = -0.47$ & $p = 0.03$) however, no significant correlation was found between EATT and the following variables; age ($r = 0.06$ & $p = 0.68$), male sex ($r = 0.02$ & $p = 0.87$), female sex ($r = -0.02$ & $p = 0.88$) and history of smoking ($r = 0.02$ & $p = 0.88$). (**Table 2**).

Table (2): Correlation between both serum adiponectin level & EATT with various clinical, biochemical and echocardiographic variables in the 2 studied groups.

Variable	S. Adiponectin level (µg/dl)		EATT (mm)	
	r-value	p-value	r-value	p-value
Age (years)	0.04	0.77 (NS)	0.06	0.68 (NS)
Male Sex	0.01	0.97 (NS)	0.02	0.87 (NS)
Female sex	- 0.01	0.96 (NS)	- 0.02	0.88 (NS)
hypertension	- 0.27	0.04 (S)	0.36	0.01 (S)
smoking	- 0.05	0.74 (NS)	0.02	0.88 (NS)
+ ve family history	- 0.28	0.04 (S)	0.036	0.01 (S)
BMI (Kg/M2)	- 0.54	0.03 (S)	0.51	0.04 (S)
WC (cm)	- 0.51	0.04 (S)	0.61	0.02 (S)
FBG (mg/dl)	- 0.44	0.02 (S)	0.41	0.04 (S)
2h PP (mg/dl)	- 0.64	0.03 (S)	0.521	0.04 (S)
HbA1C%	- 0.71	0.02 (S)	0.37	0.04 (S)
TC (mg/dl)	- 0.71	0.03 (S)	0.45	0.04 (S)
TG (mg/dl)	- 0.45	0.04 (S)	0.49	0.04 (S)
HDL-c (mg/dL)	0.12	0.04 (S)	- 0.47	0.03 (S)
LDL-c (mg/dL)	- 0.42	0.04 (S)	0.51	0.04 (S)
S. Adiponectin (µg/dl)	-----	-----	- 0.58	0.03 (S)
EATT (mm)	- 0.58	0.03 (S)	-----	-----

A significant positive correlation was found between and EATT with the mean degree of stenosis of the affected vessels ($r = 0.080$ & $p = 0.03$) while, a

significant negative correlation was found in case of serum adiponectine level ($r = -0.099$ & $p = 0.04$) (**Table 3**).

Table (3) : Correlation between both S. Adiponectin (ug/ml) level, EATT (mm) and degree of stenosis within Patient group

Degree of stenosis	S. Adiponectin ug/ml			EATT mm		
	Mean± SD	Mean± SD	r-value	p-value	Mean± SD	r-value
61.98 ± 6.90	6.068 ± 2.83	- 0.099	0.04 (S)	8.49 ± 3.06	0.080	0.03 (S)

In CAD group, EATT was found to be very significantly increased in patients with three affected vessels in comparison to those with one ($12.20 \text{ mm} \pm 1.43$ vs. $5.18 \text{ mm} \pm 1.54$, $t = 8.3669$ & $p < 0.0001$) or two affected vessels ($12.20 \text{ mm} \pm 1.43$ vs. $9.53 \text{ mm} \pm 1.40$, $t = 3.5143$ & $p = 0.0003$). Also EATT was found very significantly increased in patients with two affected arteries vs. those with one vessel affected ($9.53 \text{ mm} \pm 1.40$ vs. $5.18 \text{ mm} \pm 1.54$, $t = 6.6113$ & $p =$

0.0001). Also, serum adiponectin level was found very significantly lowered in patients with three affected vessels if compared to those with one ($2.8 \text{ } \mu\text{g/ml} \pm 0.9$ vs. $7.8 \text{ } \mu\text{g/ml} \pm 2.7$, $t = 3.1662$ & $p < 0.01$) and two affected vessels ($2.8 \text{ } \mu\text{g/ml} \pm 0.9$ vs. $6.2 \text{ } \mu\text{g/ml} \pm 2.3$, $t = 3.1480$ & $p = < 0.01$) while, no significant difference in serum adiponectin level was found between one vs. two vessels affection ($7.8 \text{ } \mu\text{g/ml} \pm 2.7$ vs. $6.2 \text{ } \mu\text{g/ml} \pm 2.3$, $t = 1.4321$ & $p = 0.291$) (**Table 4 and Figs. 4&5**).

Table (4): comparison between both s. adiponectin level , EATT and number of affected vessels within patients groups

Number of affected vessels	Serum adiponectin (µg/dl)			EATT (mm)		
	Mean ± SD	t-value	p-value	Mean ± SD	t-value	p-value
one vs. two vessels affection	7.8 ± 2.7 vs 6.2 ± 2.3	1.4321	0.291 (NS)	5.18 ± 1.54 vs 9.53 ± 1.40	6.6113	0.0001 (HS)
two vs. three vessels affection	6.2 ± 2.3 vs 2.8 ± 0.9	3.1480	< 0.01 (HS)	9.53 ± 1.40 vs 12.20 ± 1.43	3.5143	0.0003 (HS)
one vs. three vessel affection	7.8 ± 2.7 vs 2.8 ± 0.9	3.1662	< 0.01 (HS)	5.18 ± 1.54 vs 12.20 ± 1.43	8.3669	< 0.0001 (HS)

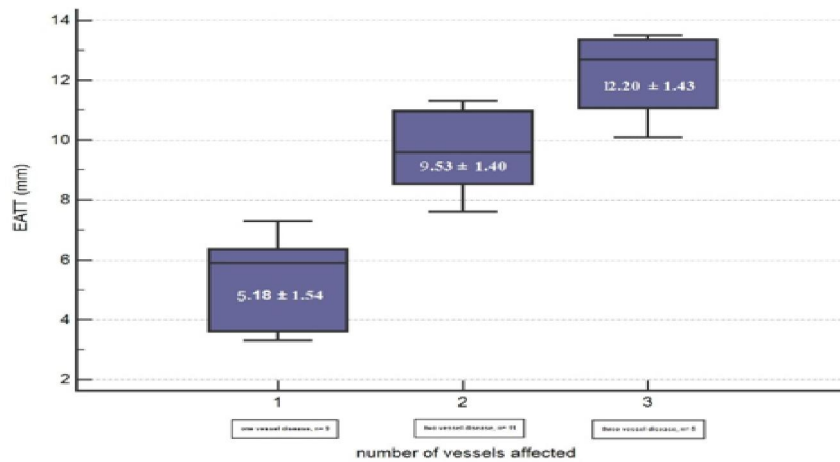


fig.4: comparison between EATT and number of the affected vessels within patients group

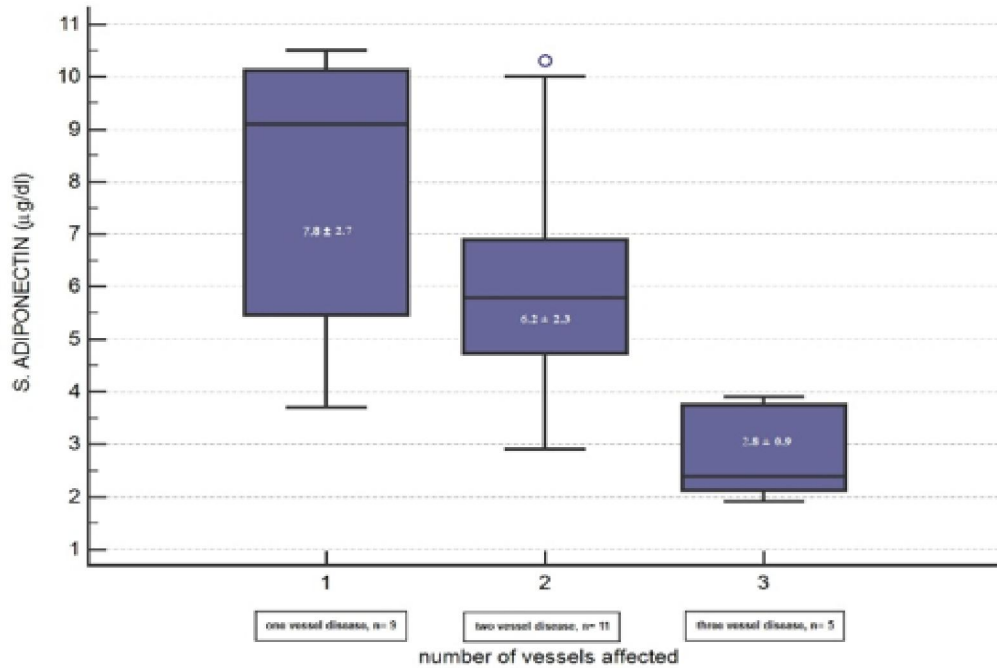


Fig. 5: comparison between s. adiponectin level and number of affected vessels within patients groups

A very significant positive correlation was found between and EATT with the Number of vessels affected within CAD group ($r = 0.8806$ & $p < 0.0001$)

while, a similar but negative very significant correlation was found in case of serum adiponectine level ($r = - 0.621$ & $p = 0.0009$) (Table 5).

Table (5) : Correlation between both S. Adiponectin (ug/ml) level, EATT (mm) and Number of vessels affected within CAD group

Number of vessels affected	S. Adiponectin ug/ml			EATT mm		
	Mean± SD	r-value	p-value	Mean± SD	r-value	p-value
1	1.84 ± 0.75	0.8806	<0.0001 (HS)	6.068 ± 2.83	- 0.621	0.0009 (HS)

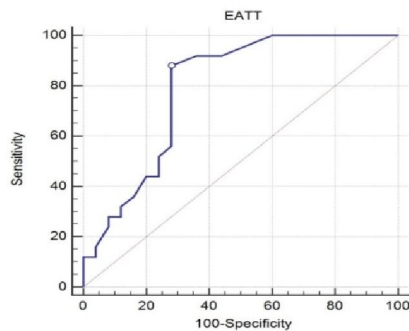
Univariate and multivariate logistic regression analyses were done between those with and without CAD to determine the independent risk factors for CAD. The results were summarized in table (6); it did not show adiponectin as an independent variable for

CAD risk on the contrary to EATT which proved its independent association with CAD to gather with all other classic independent risk factors for CAD (male sex, diabetes, hypertension,.... etc).

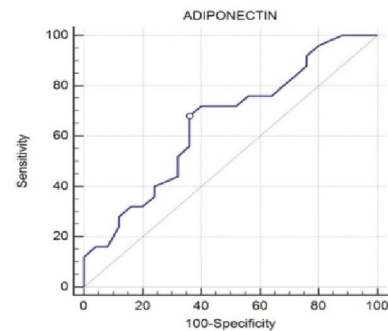
Table (6): Logistic regression analysis for the prediction of significant coronary artery disease Independent Risk Factors

CAD Independent Risk Factors	Odds ratio	CI (95%)	P value
Male sex	1.174	0.356 to 3.878	<0.0001 (HS)
diabetes	0.502	0.069 to 3.638	0.0003 (HS)
Hypertension	15.372	2.256 to 104.751	0.017 (S)
Smoking	5.755	0.540 to 61.315	<0.0001 (HS)
obesity	0.128	0.018 to 0.909	0.004 (S)
Positive family history	0.204	0.026 to 1.587	0.003 (S)
Tc (mg/dl)	1.053	1.018 to 1.090	0.003 (S)
HDL-c (mg/dl)	0.892	0.816 to 0.976	0.012 (S)
LDL-c (mg/dl)	1.128	1.032 to 1.233	0.008 (S)
TG (mg/dl)	1.029	0.990 to 1.070	0.142 (NS)
Serum Adiponectin ($\mu\text{g}/\text{dl}$)	0.889	0.710 to 1.120	0.319 (NS)
EATT (mm)	1.329	1.092 to 1.618	0.005 (s)

By using Receiver operating characteristics (ROC) curves of the EATT to predict the presence of CAD, The ROC had an area under curve (AUC) of 0.792, 95% confidence interval (CI) 0.654 to 0.894 p -value <0.0001, an EATT of > 3.7 mm predicted the presence of CAD with sensitivity of 88 %, specificity of 72 %, PPV of 75.86 % and NPV of 85.71 %. (Fig. 6).

**Fig.6: ROC curve for EATT.**

By using ROC curves of the serum adiponectin level to predict the presence of CAD, The ROC had an AUC of 0.653, 95% CI 0.505 to 0.782. p -value = 0.0514, an adiponectin serum concentration of < 6.3 $\mu\text{g}/\text{ml}$ predicted the presence of CAD with sensitivity of 68 %, specificity of 64 %, PPV of 65.38 % and NPV of 66.67 %. (Fig. 7).

**Fig.7: ROC curve for serum adiponectin level**

4. Discussion

Obesity is an inflammatory disease [15] characterized by increase in the number and size of adipocytes, associated with progressive hypoxia, up-regulation of pro-inflammatory cytokines, and chemotaxis of inflammatory cells. This phenomenon has been labeled as “adiposopathy” or sick adipose tissue [16]. According to various reports, a clear association between obesity and cardiovascular disease (CVD) has been observed [17, 18–20], relating to ectopic lipid storage, hyperglycemia, a procoagulant state, and an imbalance production of pro-inflammatory and anti-inflammatory adipokines, which mainly affect cardiovascular function [21]. In recent years, visceral adipose metabolism has proven to be important in the CVD development [22], indicating that each visceral body fat storage is anatomically and functionally different. Moreover, according to the closeness of the fat tissue to an organ, it exerts a specific local function for each one [23]. Epicardial fat is a WAT storage fat that covers 80% of the heart’s surface, representing 20% of the organ’s total weight [24]. Therefore, epicardial fat is considered to be a real VAT. This fat deposit is a major source of biomolecules and compartmentalized production of cytokines and hormones, acting as a localized gland [25]. Moreover, it regulates heart and blood vessel physiologically, via paracrine and vasocrine mechanisms. It has also been reported that epicardial adipose tissue (EAT) acts as an important energy reservoir for cardiomyocytes, which depend on fatty acid oxidation as energy source [18, 26]. Although EAT is needed for heart muscle function, in recent decades it has been published that increased thickness greatly enhances the risk of developing CVD and metabolic syndrome (MS) [27], becoming a new pharmacological target for primary and secondary prevention strategies.

In spite that standard methods of assessment of EATT are cardiac CT and MRI scans, the method of assessment of EATT used in this study was transthoracic echocardiography which has several advantages; firstly, it is relatively simple, inexpensive and readily available in almost all hospitals. Secondly, it is radio free and can be repeated as many times as required safely. On contrary to the standard cardiac CT and MRI scans which are expensive, complex in interpretation and not available except in a very few specialized centers. However, the use of echocardiography in assessment of EATT might be minimally limited by its degree of accuracy and reproducibility if compared to cardiac CT and MRI scans. Also, EAT has a 3-D structure and distribution which prevent the complete assessment by echocardiography particularly it is mere a 2-D modality. Finally, Epicardial fat volume, rather than its

thickness, may in fact be the most consistent measure of risk, as suggested [28,29]. However, we believe the limits of agreement are acceptable for screening purposes.

In Egypt, coronary cath. Labs are not available in all hospitals, expensive, require specialized trained staff therefore, necessitating the need for other easier modalities for the diagnosis and risk stratification of CAD. Thus looking for a method that may predict the presence of CAD non-invasively is greatly demanded to avoid unnecessary angiography and improve the cost effectiveness of management; the latter is a particularly important consideration in many Middle Eastern countries, including Egypt, where CAD is highly prevalent. For all these reasons, predicting the presence of CAD by noninvasive means, and to provide a tool for selecting patients for whom coronary angiography may be more beneficial represent a great value, restricting performance of coronary angiography to risky patients, and enhance the cost effectiveness management which is a particularly important consideration in many of the countries where there is no widespread availability of such facilities.

Definitely, selective coronary angiography may be cost effective and less invasive with respect to universal coronary angiography if the noninvasive tests used as a first line selection are sufficiently reliable to rule in or rule out.

Our study demonstrated that a highly significant increase in EATT among CAD patients compared to control group with An EATT of > 3.7 mm predicted the presence of CAD with sensitivity of 88 %, specificity of 72 % and Positive predictive value of 75.86 % and a negative predictive value of 85.71 %. Moreover, EATT proved its independent association with CAD as other traditionally known CAD risk factors. Also it was positively correlated to the following risk factors of CAD; hypertension, positive family history of CAD, anthropometric measurements, all glucose homeostasis parameters, TC, TG, LDL-C, degree of coronary arteries stenosis and severity of vessels affected and negatively correlated to HDL-C and serum adiponectin level.

Our findings were in agreement with the findings of *Sinha et al.*, [30] in which significant correlation was demonstrated between EAT thickness and presence of CAD ($P < 0.003$). Higher EATT was associated with severe CAD and presence of multi vessel disease. By ROC analysis, EATT >4.65 mm predicated the presence of significant coronary stenosis by 71.6% sensitivity and 73.1% specificity. Also these results were in agreement with *Eroglu et al.*, [31] showed that echocardiographic EAT thickness ≥ 5.2 mm has 85% sensitivity and 81% specificity to predict CAD. In addition, echocardiographic EAT thickness values > 3.0 mm were independently associated with the

presence of CAD.

On the contrary, there have been few reports of the correlation between EAT and the severity of CAD in a clinical setting that failed to demonstrate a statistical significance. *Chaowalit et al.*, [32]. performed clinical study to confirm the association in 139 patients; however, they failed to demonstrate the association with the severity of CAD. Similarly, *Yañez-Rivera et al.*, [33] EATT was greater in patients with CAD. However, no correlation was observed with the severity of the disease as well as serum adiponectin level.

Our study supposed that the lack of adiponectin produced by EAT may play an important role in the physiopathology of CAD by the absence or reduction of its beneficial and protective endocrine and also local paracrine effects on the cardiovascular system.

We demonstrated that serum adiponectin level was significantly lowered in CAD patients (4.06 ± 2.8 $\mu\text{g/ml}$ vs. 7.7 ± 2.8 $\mu\text{g/ml}$; $p = < 0.0001$) with an adiponectin serum concentration of < 6.3 $\mu\text{g/ml}$ predicted the presence of CAD with sensitivity of 68 %, specificity of 64 %, a Positive predictive value of 65.38 % and a negative predictive value of 66.67 %. It was in significant negative correlation with the following risk factors of CAD; hypertension, positive family history of CAD, BMI, WC, FBG, 2hpp, HbA1C%, TC, TG, LDL-C, degree of coronary arteries stenosis and severity of vessels affected, while in a positive correlation with HDL-C.

These findings were in agreement with the findings of *Kumapata et al.*, [34]. That found adiponectin levels were significantly lower in subjects with CAD. Also, adiponectin negatively correlated with BMI, FBG, 2hPP, TC, LDL-C, TG and positively with HDL-C similarly, *Kumada et al.*, [35], found plasma adiponectin levels in the CAD patients were significantly lower than those in control subjects. Also these results were in agreement with *Nakamura et al.*, and *Hara et al.* [36,37].

In contrary to our study, *Sattar et al.*, [38] had reported that there was no significant difference between baseline median adiponectin levels in CAD cases versus controls.

In our study, all parameters of glucose homeostasis (FBG, 2hPP, HbA1C %) were negatively correlated to serum adiponectin level.

Our results were in agreement with several reports that suggested a similar concepts regarding that low plasma adiponectin may be contributed to the pathogenesis of insulin resistance in some circumstances and may have a protective role against insulin resistance *Herder et al.*, *Hotta et al.*, and *Dunajska et al.* [39-41].

In term of lipid parameters our study revealed that serum TC, TG and LDL-C concentrations were

correlated negatively and significantly with the serum concentrations of adiponectin while, HDL-C level showed positive significant correlation with the serum adiponectin level. *Sattar et al.*, [38] in his prospective study stated that circulating adiponectin levels are inversely associated with triglycerides, and positively associated with blood HDL cholesterol level, also *Dunajska et al.*, [41] stated a negative correlation of adiponectin concentration with total cholesterol and triglycerides and positive correlation with HDL cholesterol concentration.

Study limitations

- The main limitation of our study is the small number of recruited patients which is modest for association studies.
- The study population consisted entirely of Egyptian patients, soother ethnic backgrounds awaits further research.
- Multi-detector computed tomography or cardiac MRI is far more sensitive and specific than echocardiography for measuring fat thickness in deeper epicardial fat layers.

Conclusion

The utilization of EATT assessment by trans-thoracic echocardiography as well as the estimation of serum Adiponectin level as a screening tests proved to serve cost effectiveness, ease of practice, instantaneous availability purposes and greatly aid in diagnosis, risk stratification and severity estimation of CAD.

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