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Measurement of Epicardial Adipose Tissue Thickness and Vitamin D Status in Obese Egyptian Adolescents and their Relationship with Cardiovascular Dysfunction

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Abstract

Background: Epicardial Adipose Tissue (EAT) is the cardiac visceral adipose tissue, influencing its structure and function, and easily assessed by trans-thoracic echocardiography. Vitamin D deficiency is prevalent among obese adolescents and is thought to affect the cardiovascular system.

Objective: This study was aimed to assess the EAT thickness (EATT) and Vitamin D status in obese adolescents to clarify their relationship with cardiovascular dysfunctions.

Patients and Methods: This was a case-control study done at the Internal Medicine Outpatient Clinics of Al-Azhar University Hospitals during the period from February 2016 to February 2018. It included 90 ado lescents divided into two equal groups; obese group (45 obese) and healthy non-obese group (45 ones). Hi story taking, clinical examination, laboratory investigations, and echocardiographic assessment were done to retrieve all relevant data.

Results: Obese adolescents were substantially different from non-obese regarding their anthropometrics w ith worse glucose homeostasis, insulin resistance and lipid profile, with a high prevalence of Metabolic Sy ndrome (MetS) (57.8%). Echocardiographically, they had a significantly increased carotid intima-media th ickness (cIMT) and EATT, higher incidence of hypertrophic cardiac remodeling, impaired systolic and dia stolic LV and RV functions. 25-Hydroxy Vitamin D (25[OH]VD) levels was lower in obese group vs. non -obese (10.2 ± 3.8 vs. 19.09 ± 7.8) respectively. EATT, cIMT, and s. Adiponectin showed the highest diag nostic capability in identification of Adolescence obesity and MetS.

Conclusion: EATT is an easily obtainable marker of cardiovascular structural and functional derangements. Vitamin D deficiency significantly worsen the cardio-metabolic risk profile and the cardiovascular function among Egyptians obese adolescents.

Keywords: Epicardial Adipose Tissue, Vitamin D, Adolescence Obesity, Cardiovascular Dysfunction.

Introduction

Throughout the past decades, the incidence of adolescent obesity has significantly increased in both developed and developing countries[1, 2]. Obesity in adolescence usually associated with considerable morbidities that hinder the quality of life[3]. These complications not only restricted to adolescence period but also extended to the adulthood which can lead to premature death[4]. Additionally, these sequels enhance the incidence of obesity in the next generations[5]. The most terrible complications associated with adolescent obesity are elevated blood pressure (BP), diabetes, dyslipidemia that constitutes in the emerging of metabolic syndrome (MetS) [6]. Hereafter, it is a strong risk factor in the developing of cardiovascular dysfunction[7]. Of note, carotid intima–media thickness (cIMT) is a strongest predictive parameter in the detection of heart attack and stroke in adulthood and is established to be increased among adolescent obese patients [8].

The epicardial adipose tissue thickness (EATT) reflects the cardiac and visceral adiposity, and it has been suggested as a new cardiometabolic risk factor owed by its close association with the myocardium status[9]. EATT contributed

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significantly in increasing the cardiovascular risk due to the capability of adipocytes in the production of interleukin-6, free fatty acids, tumor necrosis factor- α (TNF-α), and plasminogen activator inhibitor [10].

The incidence of obesity is established to be significantly associated with vitamin D deficiency (VDD) apart from vitamin D (VD) is involved in cell proliferation, differentiation, apoptosis, and angiogenesis offering a considerable explanation of the pathogenesis of various morbidities such as cardiac dysfunction, hypertension, obesity, and DM[11].

The relationship of EATT to cardiac dysfunction and cardiovascular risk factors is still not well understood, especially among obese adolescents and further research is needed before it can be used as a tool for routine clinical assessment. Moreover, the association between EATT and certain surrogate markers of atherosclerosis, such as cIMT, remains unclear. In addition, there is insufficient data on the relationship between EATT and 25[OH]VD with obesity alone or in association with other features of MetS specially in the adolescent people particularly it is well known that obesity in this age group is not uncommon, overgrowing, and predispose them to cardiovascular risk that is likely to persist during adulthood.

Therefore, this study was carried out to appreciate the association between EATT, VD status and the risk of cardiovascular dysfunction among Egyptian obese adolescents.

Patients and Methods

This case-control study included a total of 90 adolescents (12-18 years) who were attending at the Internal Medicine Outpatient Clinics of Al-Azhar University Hospitals, for evaluation of obesity as well as other recruited volunteers. This study was conducted between February 2016 to February 2018. **The study was approved by the Ethics Board of Al-Azhar University.**

This study was implemented in conformity with the declaration of Helsinki, and accordance with the ethics approved by the Ethics Unit, Faculty of Medicine, Al-Azhar University. Informed consents were obtained from the included participants and from their parents after explaining the nature of the study to all of them.

Patients were divided into two equal groups according to age and sex-specific (body mass index) BMI percentiles; obese group (45 participants), and non-obese group (45 participants).

Inclusion criteria

All apparently healthy adolescents aged 12- 18 years; presented with obesity that was documented clinically when they attained a BMI $\geq 95^{th}$ of age and sex matched percentiles and agreed to participate in the study fulfilled the inclusion criteria. Consequently, non-obese healthy adolescents were eligible for inclusion in the control group. Most of the healthy control subjects were recruited from friends, brothers & sisters of subjects included in group I as well as some of those who came for routine health care checks, proven free of illnesses and agreed to participate in this study.

Exclusion criteria

Patients with history of chronic conditions such as bronchial asthma, diabetes Mellitus (Type I or II), hypertension (HTN), psychiatric conditions, endocrinopathies causing obesity like Cushing's syndrome, and hypothyroidism were omitted from the study. Similarly, patients with syndromic obesity, cardiac dysfunction history, chronic kidney disease, chronic liver disease, acute inflammatory diseases, collagen diseases or malignant neoplasms were excluded. Additionally, patients who were receiving medications that are known to affect the tested parameters like; steroids, Vitamin D and/or calcium supplementation, weight reducing agents, anti-lipid agents, and psychotropic medications, and patients with metabolic bone disorders (including parathyroid related problems) were excluded.

Clinical and laboratory evaluation

To ensure the high levels of quality, all participants were subjected to meticulous history taking, and clinical examination to retrieve all relevant data. Hsitory taking was done to reveal the following data; age, sex, history of cardiac dysfunction, kidney disease, liver dysfunction,

diabets, endocrne diseases, cancer, and collagen diseases. Consequently, to assess the state of obesity, we evaluated the following parametrs; body weight, height, BMI, waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP) according to the age and sex- specific percentiles for each parameter.The stage of pubertal development was determined based on the Tanner staging system[12]. For each participant, a 10 ml fasting venous blood sample was withdrawn on the same day that the anthropometric data was gathered. The following variables were assessed; Fasting plasma glaucous (FPG), 2 hours post prandial plasma glucose (PPPG), glycated hemoglobin (HbA1c%), fasting insulin, homeostatic model assessment of insulin resistance (HOMA-IR), triglycerides (TG), Total cholesterol (TC), High Density Lipoprotein (HDL-c), Low Density Lipoprotein (LDL-c), 25[OH]VD, adiponectin, high sensitivity C-Reactive Protein (hs CRP), total calcium, phosphate, and alkaline phosphatase. Furthermore, liver function tests including alanine transaminase (ALT), aspartate transaminase (AST), albumin and creatinine were evaluated.

Radiological assessment

Ultrasound examination of carotid intima-media thickness (cIMT)

For measurement of intimal thickness, we assessed both carotid arteries and detection of atheromatous plaques as a marker of subclinical atherosclerosis. Radiologists scanned the right and left common carotid arteries longitudinally, and the cIMT measurement was taken in the proximal part of the common carotid artery, 1 cm proximal to the carotid bulb as the maximum distance between the intima-lumen and adventitia-media interfaces. The image was focused on the far wall (dorsal arterial wall) and image quality was optimized with gain settings. All images were taken at end diastole, incident with the R-wave. cIMT was determined as the average of 6 measurements, 3 from each of the left and right common carotid arteries.

Echocardiographic examination

Conventional transthoracic 2-D echocardiography was performed with ultrasonography (Acuson Sequoia 512 mainframe, Acuson, Mountain View, CA), using a 3.5 MHz scanning frequency phased-array transducer after 15 minutes of resting. Epicardial adipose tissue (EAT) is generally identified as the relatively echo-free space between the outer wall of the myocardium and the visceral layer of pericardium; its thickness was measured during end systole at the point on the free wall of the right ventricle (RV) along the midline of the ultrasound beam, with the best effort to be perpendicular to the aortic annulus, used as an anatomic landmark [13]. Standard M-mode recordings of left ventricle (LV) measurements, including LV dimension at end diastole (LVEDD), LV posterior wall thickness at end diastole (LVPWd) and interventricular septal thickness at end diastole (IVSd) were obtained according to the American Society of Echocardiography (ASE)[14].

The Ejection fraction (EF) was calculated using the *Teichholz method* to evaluate the systolic function of the LV [15]. LVM was calculated from the using *Devereux's formula*. The Left Ventricular Mass Index (LVMI) ($g/m^{2.7}$) was corrected for body height in meters to the allometric power of 2.7. Systolic and Diastolic functions of the LV & RV were assessed by evaluating the corresponding transvalvular (mitral or tricuspid valves) flow as well as their annular tissue velocities parameters obtained from the Pulsed Wave Doppler (PWD) & the Pulsed Wave–Tissue Doppler Imaging (PW-TDI) methods respectively, through the standard four-chamber and two-chamber views.

Statistical analysis

Statistical analysis was performed using SPSS software version 23 for Windows (SPSS Inc., Chicago, IL, USA). Normally- distributed data were exemplified in the form of Mean ± SD and the particular groups were compared using Student's t-test. Moreover, categorical variables were elucidated as number and percentage, and compared using Fisher Exact test or Chi-square test. Correlation analysis was performed using the Pearson's correlation coefficient for continuous normally distributed variables, while the Spearmann's rank correlation was used for other variables. Z-test was used to compare the statistical significance of the difference between two independent correlation coefficients to determine the strength of correlation in either groups.

Multiple regression analysis was done for detection of the independent predictors of EATT in Adolescents with MetS using X^2 and t-test analysis. Receiver operating characteristic (ROC) curve and area under ROC curve (AUC) were used to assess the diagnostic ability of biomarkers using MedCalc software version 14.8 (MedCalc Software, Mariakerke, Belgium). The optimal cut off points were calculated to maximize sensitivity and specificity. All tests were considered significant when $P < 0.05$.

Results

This study included an overall 90 candidates that were assorted into two equal groups; obese group (45 candidates) and healthy non-obese group (45 candidates) with mean age of 15.5 ± 1.6 and 15.16 ± 1.9 years in the obese, and non-obese groups, respectively. Subsequently, both groups showed substantially significant difference regarding BMI, body weight, WC, SBP and DBP ($p< 0.0001$ for each parameter). Similarly, Comparison between the two groups regarding the laboratory variables showed a statistically significant difference in glucose homeostasis parameters (FPG & HbA1c %), insulin resistance parameters (Fasting insulin & HOMA-IR), the lipid parameters (TC, LDL-c, HDL-c & TG), 25[OH]VD, iPTH, and serum adiponectin levels ($p< 0.0001$ for each parameter). Of the included subjects; 26 subjects (57.8%) out of the 45 ones included in obese group met the criteria of diagnosis of adolescence MetS while, neither the remaining 19 ones (42.2%) within group I of obese adolescents nor any of the subjects of group II did. (**Table 1).**

Table 1: Clinical and laboratory characteristics of the included participants

Variable	Obese group (n=45)	Non-obese group (n=45)	P-value
	Mean/SD (n. / %)	Mean/SD (n. / %)	
Ages (years)	15.6 ± 1.6	15.16 ± 1. 9	0.281
Weight (Kg)	84.42 ± 12.09	56.50 ± 5.40	< 0.0001
Height (M)	1.60 ± 0.06	1.60 ± 0.05	0.28
BMI (Kg/m^2)	31.50 ± 3.30	21.50 ± 1.50	< 0.0001
WC (cm)	96.7 ± 8.50	72.80 ± 4.40	< 0.0001
SBP (mmHg)	119.20 ± 6.20	110.40 ± 5.90	< 0.0001
DBP (mmHg)	74.90 ± 3.20	67.40 ± 5.70	< 0.0001
MetS	26 (57.8%)	0 (0%)	< 0.0001
FPG (mg/dl)	91.4 ± 11.6	77.04 ± 9.9	< 0.0001
PPBG (mg/dl)	131.9 ± 6.8	130.2 ± 5.1	0.17
HbA1c %	5.43 ± 0.24	5.16 ± 0.12	< 0.0001
HOMA-IR	5.3 ± 1.3	1.7 ± 0.06	< 0.0001
TG (mg/dl)	149.2 ± 18.4	138.2 ± 9.2	< 0.001
TC (mg/dl)	203.7 ± 9.2	184.4 ± 4.9	< 0.0001
LDL-c (mg/dl)	131.3 ± 11.7	99.5 ± 6.05	< 0.0001
HDL-c (mg/dl)	42.5 ± 6.2	57.2 ± 5.8	< 0.0001
25[oh]VD (ng/mL)	10.2 ± 3.8	19.09 ± 7.8	< 0.0001
iPTH (pg/mL)	57.3 ± 15.09	48.18 ± 20.8	0.021
Hs-CRP (mg/dl)	2.5 ± 0.05	0.67 ± 0.1	< 0.0001
Adiponectin (µg/mL)	9.5 ± 2.8	17.8 ± 2.08	< 0.0001

Abbreviations; **BMI**=body mass index, **WC**= waist circumference, **SBP**=systolic blood pressure, **DBP**= diastolic blood pressure, **FPG**= fasting plasma glaucous, **2HPPBG**= two hours post-prandial blood glucose, **HbA1C**= glycosylated hemoglobin, **HOMA-IR**= homeostatic model assessment of insulin resistance, **TG**= triglyceride,**TC**= total cholesterol, **LDL**= low density lipoprotein, **HDL**= high density lipoprotein , **iPTH**= intact parathormone hormone, **HS-CRP**=high sensitivity C-reactive protein.

There was a statistically significant difference between the two groups regarding cIMT , EATT, measurements of the structural dimensions of the LV including (LVEDD, LVDPWT, IVSDT), the LVM & LVMI , the systolic and diastolic function parameters obtained from the Pulsed Wave Doppler (PWD) & the Pulsed Wave–Tissue Doppler Imaging (PW-TDI) methods respectively (p< 0.0001 for each parameter). **(Table 2).**

Table 2: Comparison Between the Two Studied Groups Regarding The radiological & echocardiographic Characteristics.

Variable	Obese group (n=45)	Non-obese group (n=45)	P-value
	Mean/SD (n. / %)	Mean/SD (n. / %)	
cIMT (mm)	1.17 ± 0.27	0.56 ± 0.15	< 0.0001
EATT (mm)	8.88 ± 1.1	4.69 ± 1.41	< 0.0001
LVEDD (mm)	44.70 ± 1.77	39.17 ± 1.13	0.004
LVDPWT (mm)	10.73 ± 0.77	8.60 ± 0.76	< 0.0001
IVSDT (mm)	10.48 ± 0.33	8.85 ± 0.81	< 0.001
LVMI ($g/m^{2.7}$)	43.03 ± 7.3	38.1 ± 5.3	0.004
(M) E (cm/s)	106.82 ± 4.82	118.35 ± 4.73	< 0.0001
(M) A (cm/s)	61.94 ± 3.40	53.20 ± 2.36	< 0.0001
(M) E/A	1.7 ± 0.17	2.2 ± 0.1	< 0.0001
DT (m.sec)	224.04 ± 3.41	208.49 ± 7.80	< 0.0001
(M) E` (cm/s)	15.31 ± 1.26	18.14 ± 0.95	< 0.0001
(M) A`(cm/s)	7.5 ± 0.5	6.4 ± 0.6	0.001
(M) E`/A`	2.06 ± 0.32	2.84 ± 0.38	< 0.0001
(M) S (cm/s)	6.1 ± 0.55	9.27 ± 1.23	< 0.001
(LV) E/E`	7 ± 0.29	6.49 ± 0.13	< 0.001
(T) E` (cm/s)	13.14 ± 1.18	15.88 ± 0.67	< 0.001
(T) A` (cm/s)	13.90 ± 0.83	9.01 ± 0.84	< 0.0001
(T) E`/A`	0.91 ± 0.14	1.78 ± 0.23	< 0.0001
(T) S (cm/s)	10.82 ± 0.39	12.73 ± 0.74	0.001
(LV)MPI	0.49 ± 0.02	0.31 ± 0.01	< 0.0001
(RV)MPI	0.31 ± 0.03	0.24 ± 0.02	< 0.001
EF (%)	65.9 ± 3.9	65.7 ± 3.9	0.79
ESPAP	21.9 ± 1.06	22.4 ± 1.9	0.54

Abbreviations; **cIMT**=Carotid Intima-Media Thickness, **EATT**= epicardial adipose tissue thickness, **LVEDD**=left ventricular end diastolic volume dimension, **LVDPWT**= left ventricular posterior wall thickness at end diastole ,**IVSDT**= interventricular septal thickness at end diastole , **LVMI**= Left Ventricular Mass Index, **(M) E**=trans-mitral peak velocity of early diastolic filling , **(M) A**=trans-mitral peak velocity of late diastolic filling , **DT**=deceleration time of E wave, **(M) E`**=mitral annular early diastolic velocity, **(M) A`**=mitral annular late diastolic velocity , **(M) S**= mitral annular systolic velocity, **(T) E`**=tricuspid annular early diastolic velocity, **(T) A`**=tricuspid annular late diastolic velocity,**(T) S**=tricuspid annular systolic velocity, **LVMPI**=left ventricular myocardial performance index , **RVMPI**=right ventricular myocardial performance index , **EF**= ejection fraction, **ESPAP**= Estimated Pulmonary Artery Systolic Pressure .

Having the obese group, there were a statistically significant correlation between the levels of VD and BMI (r=- 0.97, p< 0.0001), WC(r=- 0.96, p< 0.0001), SBP(r=- 0.96, p< 0.0001), DBP(r=- 0.95, p< 0.0001 EATT(r=- 0.95, p< 0.0001), and cIMT(r=- 0.96, p< 0.0001). Moreover, VD showed statistically significant correlation with the levels of TG (r=0.73, p< 0.000), TC (r=- 0.61, p< 0.000), LDL (r=-0.59, p< 0.0001), cIMT(r=- 0.97, p< 0.0001), and EATT(r=- 0.96, p< 0.0001) in the non-obese group. Consequently, the levels of EATT showed significant correlation with the level of BMI (r=0.96, p< 0.0001), WC(r=0.97, p< 0.0001), SBP(r=0.96, p< 0.0001), DBP(r=0.97,

p< 0.0001), fasting insulin(r=0.92, p< 0.0001), and cIMT(r=0.99, p< 0.0001), among the obese group. Furthermore, among non-obese group, EATT as significantly correlated with the levels of TG (r=0.73, p< 0.0001), TC (r=0.62, p< 0.0001), adiponectin (r=- 0.96, p< 0.0001), and cIMT (r=- 0.99, p< 0.0001) **(Table 3).**

Table 3: correlations between 25[OH]VD levels & EATT with clinical, laboratory & radiological variables among subjects of both studied groups

Variables	25[OH]VD (ng/ml)				EATT (mm)			
	Obese group		Non-obese group		Obese group		Non-obese group	
	r value	P value	r value	P value	r value	P value	r value	P value
BMI (Kg/m^2)	- 0.97	<0.0001*	0.16	0.28 **	0.96	<0.0001*	0.21	0.18 **
WC (Cm)	- 0.96	<0.0001*	0.06	0.70 **	0.89	<0.0001*	- 0.09	0.58 **
SBP (mmHg)	- 0.96	<0.0001*	0.05	0.75 **	0.97	<0.0001*	- 0.11	0.48 **
DBP (mmHg)	- 0.95	<0.0001*	0.03	0.85 **	0.96	<0.0001*	- 0.07	0.63 **
FPG (mg/dl)	- 0.97	<0.0001*	0.09	0.55 **	0.97	<0.0001*	- 0.04	0.81 **
2hppbs (mg/dl)	- 0.93	<0.0001*	0.05	0.75 **	0.93	<0.0001*	- 0.05	0.73 **
HbA1C%	- 0.87	<0.0001*	0.05	0.73 **	0.87	<0.0001*	- 0.01	0.97 **
F. insulin (µIU/ml)	- 0.92	<0.0001*	0.15	0.32 **	0.92	<0.0001*	0.22	0.15 **
HOMA-IR	- 0.95	<0.0001*	0.11	0.47 **	0.95	<0.0001*	0.18	0.30 **
TG (mg/dl)	- 0.96	<0.0001*	- 0.69	<0.0001*	0.96	<0.0001*	0.73	<0.0001*
TC (mg/dl)	- 0.98	<0.0001*	- 0.61	<0.0001*	0.98	<0.0001*	0.62	<0.0001*
HDL-c (mg/dl)	0.97	<0.0001*	0.88	<0.0001*	- 0.97	<0.0001*	-0.89	<0.0001*
LDL-c (mg/dl)	- 0.98	<0.0001*	- 0.59	<0.0001*	0.98	<0.0001*	0.70	<0.0001*
25[OH]VD (ng/ml)	1	1	1	1	- 0.95	<0.0001*	- 0.96	<0.0001*
iPTH (pg/ml)	- 0.98	<0.0001*	- 0.96	<0.0001*	0.98	<0.0001*	0.95	<0.0001*
H.S. cRP (mg/dl)	- 0.93	<0.0001*	- 0.27	0.08**	0.93	<0.0001*	0.27	0.08 **
Adiponectin (µg/ml)	0.96	<0.0001*	0.95	<0.0001*	- 0.96	<0.0001*	- 0.96	<0.0001*
cIMT (mm)	- 0.96	<0.0001*	- 0.97	<0.0001*	0.99	<0.0001*	0.87	<0.0001*
EATT (mm)	- 0.95	<0.0001*	- 0.96	<0.0001*	1	1	1	1
LVM (g)	- 0.91	<0.0001*	- 0.90	<0.0001*	0.96	<0.0001*	0.93	<0.0001*
LVMI (g/m$^{2.7}$)	- 0.73	<0.0001*	- 0.80	<0.0001*	0.80	<0.0001*	0.84	<0.0001*
(M) E/A	0.97	<0.0001*	0.98	<0.0001*	- 0.99	<0.0001*	- 0.95	<0.0001*
DT (m.sec)	- 0.96	<0.0001*	- 0.99	<0.0001*	0.95	<0.0001*	0.97	<0.0001*
(M)E'/A'	0.97	<0.0001*	0.94	<0.0001*	- 0.97	<0.0001*	- 0.94	<0.0001*
(M) S (cm/s)	0.97	<0.0001*	0.94	<0.0001*	- 0.98	<0.0001*	- 0.94	<0.0001*
(LV)E/E'	- 0.90	<0.0001*	- 0.51	0.0004*	0.89	<0.0001*	0.55	<0.0001*
(T) E'/A'	0.98	<0.0001*	0.98	<0.0001*	- 0.98	<0.0001*	- 0.96	<0.0001*
(T) S (cm/s)	0.98	<0.0001*	0.97	<0.0001*	- 0.98	<0.0001*	- 0.91	<0.0001*
(RV) MPI	- 0.94	<0.0001*	- 0.77	<0.0001*	0.99	<0.0001*	0.93	<0.0001*
(LV) MPI	- 0.93	<0.0001*	- 0.77	<0.0001*	0.97	<0.0001*	0.85	<0.0001*
EF%	- 0.05	0.76 **	- 0.09	0.66 **	0.004	0.978 **	0.21	0.18 **
ESPAP (mmHg)	- 0.10	0.53 **	- 0.07	0.64 **	0.05	0.763 **	- 0.04	0.81 **

Abbreviations; **BMI**=body mass index, **WC**= waist circumference, **SBP**=systolic blood pressure, **DBP**= diastolic blood pressure, **FPG**= fasting plasma glaucous, **2HPPBG**= two hours post-prandial blood glucose, **HbA1C**= glycosylated hemoglobin, **HOMA-IR**= homeostatic model assessment of insulin resistance,**TC**=total cholesterol, **TG**= triglyceride, **LDL**= low density lipoprotein, **HDL**= high density lipoprotein , **iPTH**= intact parathormone hormone, **HS-CRP**=high sensitivity C-reactive protein, **cIMT**=Carotid Intima-Media Thickness,**EATT**= epicardial adipose tissue thickness, **LVEDD**=left ventricular end diastolic volume dimension, **LVDPWT**= left ventricular posterior wall thickness at end diastole ,**IVSDT**= interventricular septal thickness at end diastole , **LVMI**= Left Ventricular Mass Index, **(M) E**=trans-mitral peak velocity of early diastolic filling , **(M) A**=trans-mitral peak velocity of late diastolic filling , **DT**=deceleration time of E wave, **(M) E`**=mitral annular early diastolic velocity, **(M) A`**=mitral annular late diastolic velocity , **(M) S**= mitral annular systolic velocity, **(T) E`**=tricuspid annular early diastolic velocity, **(T) A`**=tricuspid annular late diastolic velocity,**(T) S**=tricuspid annular systolic velocity,**LVMPI**=left ventricular Myocardial Performance Index , **RVMPI**=right ventricular Myocardial Performance Index , **EF**= ejection fraction, **ESPAP**= Estimated Pulmonary Artery Systolic Pressure .

Multivariate prediction analysis model was done to delineate the independent predictors of EATT in adolescents with MetS subgroup and showed that; only cIMT achieved statistically significant ability in prediction of EATT (R=0.75, P=0.02) **(Figure.1).**

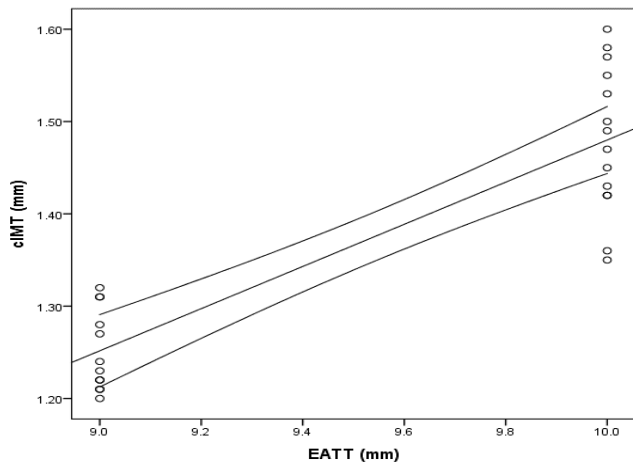

Fig.1: The ability of cIMT in the prediction of EATT among patients with metabolic syndrome.

Having receiver operating characteristics curve (ROC) analysis, of EATT, cIMT, HOMA-IR and s.Adiponectin showed high diagnostic ability in the detection of obesity with specificity of 71.1%, 73.3%, 77.8%, and 88.9%, respectively **(Figure.2)**.

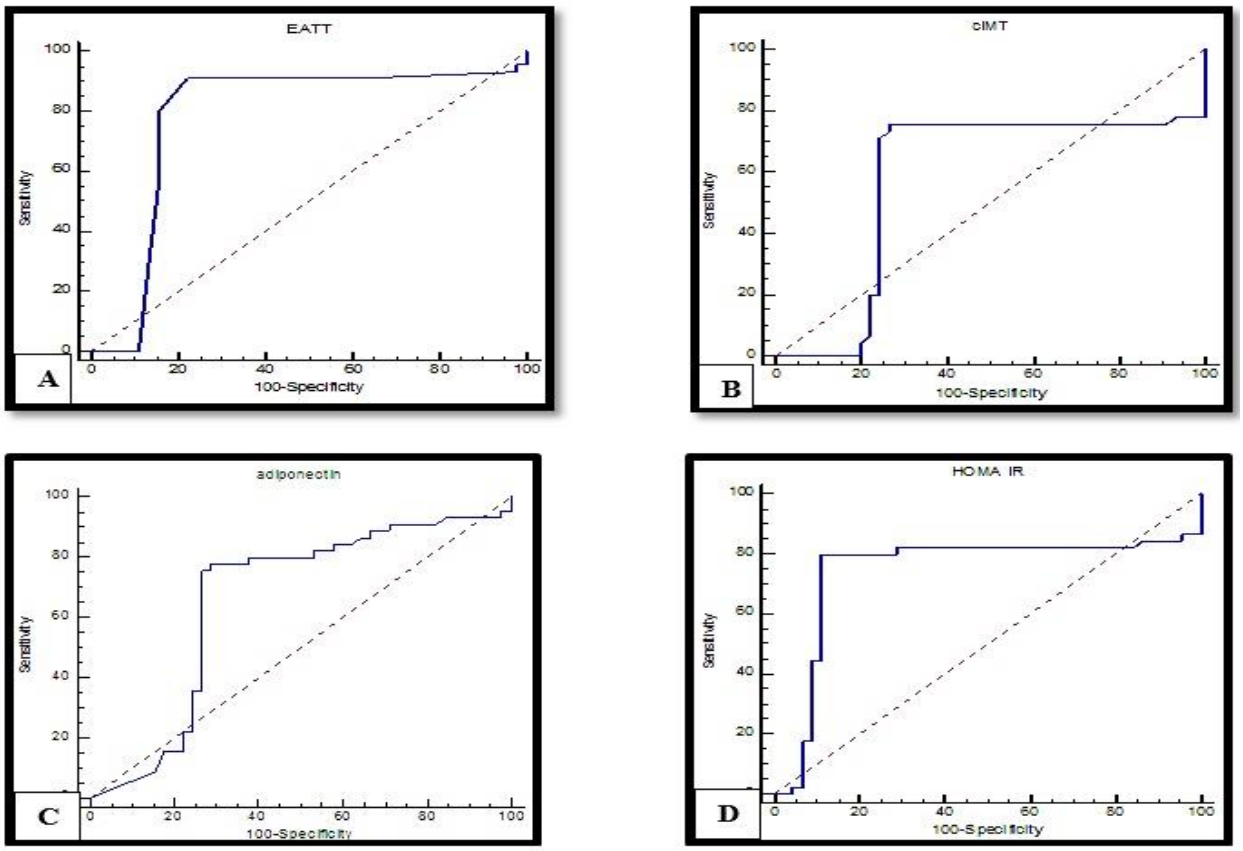

Fig. 2: Receiver operating characteristics (ROC) curves showing the diagnostic ability of **(A)** EATT, **(B**) cIMT **,(C)** s.Adiponectin **(D)** HOMA-IR for predicting adolescence obesity.

Furthermore, EATT, cIMT, HOMA-IR and s.Adiponectin showed high diagnostic ability in the detection of Mets with specificity of 77%, 82%, 85.4%, and 93.4%, respectively**. (Table.4)**

Table 4: Cutoff values, specificity, and sensitivity of EATT, cIMT, HOMA-IR & s.Adiponectin in prediction of Adolescence obesity and metabolic syndrome.

	variable	s.Adiponectin	cIMT	EATT	HOMA-IR
Adolescence obesity	**AUC**	0.65	0.57	0.78	0.74
	Cut-off value	13.49 (µg/ml)	0.76 (mm)	6 (mm)	3.4
	Sensitivity (%)	77.7	75.6	91.1	80
	Specificity (%)	71.1	73.3	77.8	88.9
	(+ve) Likelihood ratio	0.31	2.83	4.10	7.20
	(-ve) Likelihood ratio	2.69	0.33	0.1	0.2
	PPV (%)	23	23.9	31.3	44.4
	NPV (%)	96.6	96.4	98.7	97.6
Adolescence Metabolic syndrome	**AUC**	0.7	0.54	0.77	0.67
	Cut-off value	10.09 (µg/ml)	1.05 (mm)	8 (mm)	5.1
	Sensitivity (%)	86.2	69	88.46	69
	Specificity (%)	77	82	85.4	93.4
	(+ve) Likelihood ratio	3.76	3.82	18.23	10.5
	(-ve) Likelihood ratio	0.18	0.38	0.1	0.33
	PPV (%)	29.4	29.8	66.9	96.4
	NPV (%)	98	96	98.8	53.9

Abbreviations; **EATT**= epicardial adipose tissue thickness, **cIMT**= Carotid Intima-Media Thickness, **HOMA-IR**= homeostatic model assessment of insulin resistance **AUC**= area under curve, **PPV**= positive predictive value, **NPV**= negative predictive value,

Discussion

Obesity is a multifaceted health problem with multisystem consequences and its spectrum not restricted to adulthood. Occurrence of obesity during adolescence and its persistence during the adulthood usually exists and is contributing significantly in increasing the risks of various morbidities and mortalities related to cardiac dysfunction[16].

The evidence retrieved in our study illustrated that; obese adolescents were different substantially from non-obese adolescents regarding their anthropometric measurements, laboratory, and echocardiographic structural and functional parameters with a high prevalence of cardiometabolic risk factors including; elevated BP, impaired fasting glucose & glucose tolerance, insulin resistance. Moreover, the prevalence of metabolic syndrome was (57.8%). They exhibited also a subtle, sub-diagnostic, impairment of both systolic and diastolic functions **(Tables 1&2)**.

This confirms our postulation that early onset obesity tends to affect the cardiovascular system adversely by creating a set of different pathological processes including premature and accelerated wide-spread thermogenesis, low grade generalized inflammatory reactions that impair the endothelial functions, impaired metabolic pathways leading to insulin resistance and dyslipidemia, alteration in the humoral factors released from the adipose tissue , the adipokines, with increased synthesis and release of the harmful adipokines as well as the pro-inflammatory cytokines in association with down regulation of the protective ones. All of the aforementioned mechanisms culminated the impairment of cardiovascular functions as well as the adverse geometrical remodeling detected among obese adolescents included in our study.

Despite BMI is feasible procedure in the assessment of patients at high risk of cardiometabolic dysfunction, it does not discriminate the distribution of body fat as it reflects only fat and lean body masses[17].Thereafter, assessment of visceral adiposity as the abdominal adiposity using EATT is more crucial than general adiposity[18].

For that, we chose the EAT as an interesting depot of visceral adipose tissue with close proximity to the heart to study its impact on the myocardial structure and functions trying to reproduce the utility of measuring its thickness by transthoracic echocardiography as an easily

obtainable, non-invasive and reproducible method for evaluating the underlying cardiometabolic state in obese adolescents trying to illustrate the role of visceral adiposopathy in cardiometabolic dysfunction.

Our results pointed to the usefulness of EATT measurement as an indicator of cardiovascular structure and function supported by many statistical evidences; firstly, EATT was found to be significantly higher in obese adolescents compared to the non-obese ones. Secondly, EATT showed a statistically significant positive correlations with all the cardiometabolic risk factors including obesity, elevated BP, impaired fasting glucose & glucose tolerance, insulin resistance, cIMT which is a marker of subclinical atherosclerosis, the deterioration of both systolic and diastolic functions **(Table 3)**. Thirdly, EATT showed high diagnostic ability in the detection of adolescence obesity and MetS at cut off values (6mm) & (8mm) respectively with sensitivity of 91.1% and specificity of 77.8% in case of obesity while with sensitivity of 88.46% and specificity of 85.4% in case of adolescence MetS **(Table 4)**.

Our results were concomitant with previous studies. For instance, Elshorbagy *et al*, notified that; EATT showed significant correlation with the anthropometric parameters such as BMI, and WC and laboratory variables such as fasting insulin, TG, and Hs-CRP among obese group and specially in patients with MetS[19]. Moreover, this results also in conformity with Akyol *et al*. that illustrated the presence of cardiometabolic dysfunction with increased EATT, cIMT , LVMI, and MPI were found in adolescents obese patients [20].

Our study have found in the multivariate prediction analysis model that was done to delineate the independent predictors of EATT in adolescents with MetS subgroup that; only cIMT achieved statistically significant ability in prediction of EATT (R=0.75, P=0.02).

The significant correlation between EATT and cIMT brings to light that; EATT is a promising biomarker in assessment of cardiac dysfunction relative to WC, and BMI among adolescent's obese patients owed by its close relation to the severity of carotid artery stiffness, and endothelial dysfunction[21] .However, this result should by subjected to further evaluation.

VDD was associated with obesity and related diseases that hinder patient's quality life[22]. In our work, the levels of VD showed significant negative correlations with all the cardiometabolic risk factors including obesity, elevated BP, impaired fasting glucose & glucose tolerance, presence of MetS, insulin resistance, cIMT, the deterioration of both systolic and diastolic functions among the adolescents obese group.

Our result was in conformity with previous studies. Pacifico *et al.* illustrated the significant association of VD levels and obesity, elevated blood pressure, and MetS[23]. The underlying mechanism is a doubtful issue despite the numerous studies that showed the inverse association between VD levels and body fat mass, elevated BP, elevated glaucous, and TG level[24, 25].However, the inverse correlation between VD levels and insulin resistance may provide a possible explanation[26]. Furthermore, it was established that obesity is associated with insulin resistance, low HDL, TC, and high LDL. However, VDD may be a sequel of obesity itself[27]. Throughout the past era, it was suggested that VD has a protective role against cardiovascular dysfunction, [28] our results were agreed with the previous evidence particularly with the close association of VD levels and the echocardiological parameters. This result may be explained due to the reno-protective function (suppression of renin angiotensin system), and its roles in calcium metabolism, and on the vascular wall [28].

To the best of our knowledge, no previous study had investigated the possible association between EATT and the level of 25[OH]VD particularly in adolescence. Under this condition, we demonstrated for the first time an evidence of the inverse relationship between those 2 parameters in the obese adolescent population.

In contrast to our findings, Utku *et al*. studied the relationship between EATT and VD in patients with metabolic syndrome and found that EATT increased in patients with metabolic syndrome. In contradiction to literature; the levels of 25[OH]VD was not found to be low in patients with metabolic syndrome. Any significant correlation was not found between EATT and 25[OH]VD levels. However, this study was conducted on adults with their mean of ages is 38.5±9.7 [29].

Limitations of our study

The main limitation of the present study is the smaller sample size that prevented the conduction of further subgroup analysis particularly we demonstrated the presence of the different obesity phenotypes among the obese group. Further large-scale studies with larger sample size are warranted to solve this issue. Another limitation encountered is that we were not taking the seasonal variations during sampling for 25[OH]VD levels in consideration which is a known factor that can affect the 25[OH]VD level assay.

Conclusions

It is of interest and is not redundant to use EATT as a marker for the adverse metabolic state and cardiovascular dysfunction among obese adolescents; VD deficiency is closely related to the classical cardiometabolic risk factors including obesity, elevated blood pressure, diabetes mellitus and prediabetes, dyslipidemia during the adolescence. Therefore, obese adolescents should be subjected to close monitoring and high levels of health care to avoid short term, and long-term cardiometabolic dysfunctions.

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