The Association of Epicardial Adipose Tissue and the Metabolic Syndrome in Community Participants in South Africa

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**Abstract**

**Background:** We sought to determine the association of echocardiographically derived epicardial adipose tissue (EAT) thickness, which is a component of visceral adipose tissue, with the metabolic syndrome (MetS) in a cohort of randomly selected community participants. **Methods:** South African-Asian Indians aged 15–64 years were recruited over a 2-year period after informed consent was obtained. All participants who had complete measurements done for biochemistry and echocardiography (using established criteria), were dichotomized into the MetS or non-MetS groups defined according to the harmonized criteria. **Results:** Of the 953 (232 men and 721 women) participants recruited, 47.1% (448) were classified with the MetS. These participants had larger waist circumference and body mass index ($P < 0.001$), with larger LA volumes and diameter, thicker ventricular walls, higher left ventricular mass, relative wall thickness, and EAT ($P < 0.001$). There was a corresponding increase in EAT thickness with increasing number of MetS risk factors at the transition from 0 MetS factors to 1 (95% confidence interval [CI] −0.8; −0.2) and from 2 to 3 MetS factors (95% CI −0.9; −0.4). The AUC of the receiver operator curve was highest for triglycerides (0.845), followed by fasting plasma glucose (0.795) and then EAT (0.789). An EAT value of <3.6 mm predicted the presence of the MetS with a 78% sensitivity and 70% specificity. Using backward stepwise logistic regression, the most significant independent determinants of the MetS after adjusting for age, gender, and type 2 diabetes mellitus, was fasting plasma glucose (odds ratio [OR] = 1.2), triglycerides (OR = 7.1), and EAT (OR = 2.3). **Conclusion:** Although EAT is associated with the MetS, and can identify individuals at increased cardiometabolic risk, it has a limited additional role compared to current risk markers.

**Keywords:** Echocardiography, epicardial adipose tissue, metabolic syndrome, visceral obesity

**Introduction**

The metabolic syndrome (MetS) is characterized by cardiometabolic risk factor clustering and is associated with an increased risk for the development of coronary artery disease. Visceral obesity is regarded as one key proponent in the pathophysiology of the MetS since visceral adipose tissue is metabolically active. Although the waist circumference is a surrogate measurement of visceral fat and was found to be the main driver for the development of the MetS in a community of Asian Indians in KwaZulu-Natal, South Africa, its limitation lies in its inability to delineate subcutaneous from visceral fat. Magnetic resonance, computed tomography (CT), and densitometry provide a more precise quantification of visceral fat but are not feasible for screening due to higher costs, increased risk, or lesser availability.

Epicardial adipose thickness (EAT) which is a component of visceral adipose tissue and correlates strongly with visceral abdominal fat, increases with obesity, and has also been associated with the clinical parameters of the multiple sclerosis (MS), as well as anthropometric (body mass index and waist circumference), insulin resistance, and obesity. EAT may be echocardiographically derived, and by comparison to other modalities, is inexpensive, noninvasive, and readily available but still accurate and reproducible, and has been validated using magnetic resonance imaging and CT. However, there are currently no standardized EAT cut points which could be used to identify the MetS since there is little data available in non-Caucasians. Another reason is the large degree of variation of EAT thickness among the different

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Methods: The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (University of KwaZulu-Natal Biomedical Research Ethics Committee/Ref. BE 172/09) and with the Helsinki Declaration of 1975, as revised in 2000.

Study design
This study was a prospective, cross-sectional study of randomly selected participants in the Phoenix community, in Durban, KwaZulu-Natal. The full methodology has been reported previously[15] (CVJA, Clinical reviews). Briefly, this project is part of a subanalysis of the Phoenix Lifestyle Project cohort, and South African-Asian Indians aged 15–64 years were recruited over a 2-year period (January 2007–December 2008). Individuals within the target age group were randomly selected using the Kish method of sampling. This method documents household members and selects one to be included in the study. All participants who had complete measurements done for biochemistry and echocardiography were dichotomized into the MetS or non-MetS groups defined according to the harmonized criteria.[16]

Each patient underwent a transthoracic 2D-guided M-mode echocardiogram and a comprehensive Doppler echocardiogram. Echocardiograms were performed with a Siemens CV70 instrument (Siemens, New York, NY, USA) using a 3.5 MHz transducer with patients lying in the left lateral decubitus position. M-Mode measurements were performed for the measurements of the aortic root and left atrial (LA) size according to published guidelines, as were chamber dimensions.[17] The left ventricular (LV) internal dimensions and the thickness of the posterior and septal wall were measured according to published guidelines.[17] The LV mass (LVM) was estimated using the M-mode-derived cubed method and divided by height[6-7] to correct for body habitus[18] (LVM index).

The ejection fraction (EF) was measured using a monoplanar image in the four-chamber view, by tracing the contours of the LV internal diameter during peak systole and peak diastole. The EF was calculated automatically by computer software using the Simpson’s formula.

Subepicardial adipose tissue thickness measurement
The thickness of the epicardial fat was measured in the free wall of the right ventricle in the parasternal long and short axis as proposed by[10] Iacobellis et al. during end diastole. Epicardial adipose tissue appears as an echo-free or hyperechoic space and has been validated as an indicator of visceral fat.[10] The right ventricle was chosen in the long-axis view for the measurement of epicardial fat, as this point is recognized as having the highest absolute thickness of the epicardial fat.[19] The parasternal long-axis and short-axis views allow the most accurate measurement of epicardial adipose tissue on the right ventricle, with the best cursor-beam orientation in each view [Figure 1].[10]

All echocardiographic measurements were averaged over three consecutive cardiac cycles, measured by a single investigator (DRP) who was blinded to all other variables.

Intraobserver variability
It is established that intraobserver variability is low, when the echocardiograms are performed by one experienced echocardiographer,[20] as is the case in our study. Furthermore, each measurement was performed according to the European Society of Echocardiography guidelines to ensure standardization. At least 3 cycles were recorded and the average was documented. Measurements of EAT thickness was made at two sites and an average of 3 cycles at these two sites were taken.

Statistical analysis
Raw data were cleaned and transferred onto an SPSS software package Version 25 (SPSS, Chicago, IL, USA). All data are expressed as mean ± standard deviation. The LV mass was indexed to height. Chi-square testing and one-way ANOVA were used to calculate the statistical differences of anthropometric, biochemical, and echocardiography variables between patients with and without the MetS. Pearson’s correlation analysis was used to determine the relationship between EAT and other variables. Stepwise multiple regression was performed to ascertain the independent risk factors of the MetS, after adjusting for all other variables. A receiver operator curve (ROC) was constructed, with corresponding sensitivity and specificity values, to determine cut points for the presence of the MetS. P < 0.05 were considered statistically significant.

Results
Measurement of intraobserver variability was calculated from samples recorded on the same subject at different intervals. A coefficient of variance of 4%, 5%, 4%, 4%, and 9% was found for the mean LA, LVM, EDD, EF, and EAT measurements, respectively.

The baseline characteristics of the 953 (232 men and 721 women) participants, classified into those with and without MetS, are shown in Table 1.

There were statistically significant differences (P < 0.05) for all clinical, biochemical, and echocardiography parameters tested. Patients with MetS were older, with larger waist circumference and body mass index (BMI). By definition, fasting plasma glucose levels, HOMA-IR, serum cholesterol,
triglycerides, and low-density lipoprotein (LDL) levels were significantly higher in patients with the MetS, with high-density lipoprotein (HDL) levels were significantly lower [Table 1].

Patients with the MetS also had larger LA volumes and diameter, thicker ventricular walls, higher LV mass, and relative wall thickness (RWT) ($P < 0.001$). The EAT was also significantly thicker ($P < 0.001$). There was no difference in the EF between the two groups ($P = 0.620$).

There was a corresponding increase in EAT thickness as the number of MetS risk factors increased [Figure 1], with significant changes seen during two points: The transition from 0 MetS factors to 1 (95% confidence interval [CI] −0.8; −0.2) and from 2 to 3 MetS factors (95%CI −0.9; −0.4).

A highly significant correlation was shown between EAT and anthropometry measures (highest $r$ values for waist circumference and BMI, respectively), as well with all other biochemical and echocardiography variables, with the exception of the HBA1c [Table 2].

A ROC was constructed to determine the discriminating capacity of the parameters above to identify the MetS. The highest area under the curve [Table 3] was taken by triglycerides (0.845), followed by fasting plasma glucose (0.795) and then EAT (0.789). An EAT value of <3.6 mm predicted the presence of the MetS with a 78% sensitivity and 70% specificity [Figure 2].

Using backward stepwise logistic regression [Table 4], the independent determinants of the MetS were investigated.

### Table 1: Baseline anthropometry, biochemistry, and echocardiography characteristics of the sample

|                          | All ($n=953$) | No MetS ($n=505/52.9\%$) | MetS ($n=448/47.1\%$) | $P^*$ | 95% CI       |
|--------------------------|--------------|--------------------------|-----------------------|------|-------------|
| Age                      | 43.8±13.1    | 40±14                    | 49±9                  | <0.001 | −11.7--8.7 |
| Men                      | 232          | 140 (60.3%)              | 92 (59.7%)            | 0.01  | −0.13--0.017|
| Women                    | 721          | 365 (50.6%)              | 356 (49.4%)           | 0.079 | −0.104--0.006|
| Smokers                  | 232          | 134 (57.8%)              | 98 (42.2%)            | 0.079 | −0.104--0.006|
| BMI                      | 27.4±6.4     | 25.5±6.26                | 29.9±5.6              | <0.001 | −5.3--3.8   |
| Waist                    | 92.9±15.3    | 86.7±15.2                | 99.1±11.4             | <0.001 | −14.1--10.5 |
| Blood pressure           |              |                          |                       |       |             |
| Mean systolic            | 132.8±23.5   | 124.8±17.7               | 142.2±24.9            | <0.001 | −21.9--16.3 |
| Mean diastolic           | 81.6±12.3    | 76.9±10.9                | 85.9±11.9             | 0.052 | −10.9--7.9  |
| Biochemistry             |              |                          |                       |       |             |
| Fasting plasma glucose   | 6.4±2.9      | 5.2±1.8                  | 7.7±3.5               | <0.001 | −2.8--2.1   |
| HOMA-IR                  | 5.2±14.6     | 3.3±10.8                 | 7.3±17.7              | <0.001 | −5.9--2.2   |
| Serum cholesterol        | 5.5±1.2      | 5.3±1.1                  | 5.8±1.1               | <0.001 | −0.8--0.5   |
| Triglycerides            | 1.8±2.7      | 1.3±0.7                  | 2.4±3.6               | <0.001 | −1.6--0.9   |
| HDL cholesterol          | 1.3±0.45     | 1.4±0.4                  | 1.2±0.5               | <0.001 | 0.14-0.25   |
| LDL cholesterol          | 3.3±1.03     | 3.2±1.04                 | 3.6±1.0               | <0.001 | −0.46-0.19  |
| Echocardiography         |              |                          |                       |       |             |
| LVEDD                    | 46.5±5.3     | 46±5                     | 47±6                  | 0.01  | −1.9--0.53  |
| LA                       | 34.6±6.8     | 33.3±6.3                 | 36.1±7.1              | <0.001 | −1.9--0.53  |
| LAVI                     | 1.3±0.3      | 1.2±0.3                  | 1.3±0.3               | <0.001 | 0.09-0.17   |
| LV mass                  | 123.6±49.3   | 117±40                   | 141±53                | <0.001 | −3.7--2.2   |
| LVMI                     | 35.2±14.0    | 30.9±11.5                | 40.0±15.0             | <0.001 | −10.8--7.4  |
| RWT                      | 0.28±0.09    | 0.27±0.09                | 0.3±0.09              | <0.001 | −0.05--0.03 |
| Ejection fraction        | 69.3±8.7     | 69±8                     | 69±9                  | 0.433 | −0.66--1.6  |
| EAT^                      | 3.8±0.9      | 3.3±0.9                  | 4.2±0.7               | <0.001 | −1.0--0.8   |

*Between MetS and no MetS, ^Average of PLAX and PSAX subepicardial adipose tissue measurement. LVEDD=Left ventricular end-diastolic dimension, RWT=Regional wall thickness, CI=Confidence interval, BMI=Body mass index, HOMA-IR=Homeostatic model assessment-insulin resistance, HDL=High-density lipoprotein, LDL=Low-density lipoprotein, LAVI=Left atrial volume index, LA=Left atrial, LVMI=Left ventricular mass index, MetS=Metabolic syndrome, EAT=Epicardial adipose tissue
The parameters used were the BMI, waist circumference, fasting plasma glucose, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, LA size, RWT, LV mass, and EAT. After adjusting for age, gender, and type 2 diabetes mellitus, the age, waist circumference, fasting plasma glucose, triglycerides, HDL, and EAT emerged as independent predictors of the MetS. An increase in 1 unit (mmol/l) of triglycerides was associated with a sevenfold increase for the development of the MetS, followed by EAT (odds ratio [OR] = 2.3) and fasting plasma glucose (OR = 1.2).

**Discussion**

This study determined EAT thickness using echocardiography in individuals with a high cardiovascular risk profile and the MetS in order to determine the value of EAT in the identification of the MetS. There is limited information available on EAT derived from echocardiography, particularly in non-Caucasian ethnic groups. Furthermore, from the existing data, sample sizes have been generally small\[21-23\] in comparison to the current study of 953 participants from a community-based sample.

To the author’s knowledge, the present study is the first to measure epicardial fat tissue (EAT) thickness echocardiographically in South African participants and confirmed the significantly increased thickness of epicardial fat in patients with MetS as compared to those without (P < 0.005), as has been reported in the literature.\[14\] EAT thickness has been validated as a measure of visceral adiposity\[9\] and has been shown to provide a more accurate assessment of metabolic risk, which could not be accounted for by anthropometric indexes and intra-abdominal visceral fat.\[24\] The increased risk for the development of coronary artery disease in patients with MetS may be explained by the lack of fascia-like structures separating the EAT from the myocardium, as both share the coronary supply,\[25,26\] which allows direct intercommunication between endothelium and adipokines. Furthermore, the initiation and expansion of coronary disease in MetS may be due to an imbalance in epicardial VAT expression between pro-atherogenic leptin and anti-atherogenic adiponectin.\[27\]

A highly significant correlation was shown between EAT and anthropometry measures, particularly the waist circumference, and this was expected, as EAT is a component of visceral adipose tissue, which increases in the MetS. There was also a significant association with echocardiographic parameters, with a positive correlation between EAT and LA, LV dimension, as well as with the RWT. It appears that EAT reflects the structural changes in the heart associated with obesity, and our findings are in keeping with previous studies in the literature.\[9,28\]
Our study shows that EAT thickness increases with increasing number of MetS components. A similar finding was reported by Bettencourt et al., where quartiles of increasing epicardial fat were associated with increasing prevalence of diabetes. This may be attributed to the numerous inflammatory cytokines secreted by EAT due to its lipogenic qualities as compared to other types of fat tissues of the body.

The AUC was highest for triglycerides for the discrimination of the MetS. This was followed by the fasting plasma glucose and then EAT, which predicted the presence of the MetS with a 78% sensitivity and 70% specificity at a value of 3.6 mm. This cut point was much lower than has been reported in a study of Caucasians, where cut points of 9.5 mm and 7.5 mm were found in men and women, respectively, and 6.0 ± 2.0 mm in a sample in Turkey. This finding is most likely due to the higher volume of EAT in Caucasians compared to other ethnic groups, underscoring the ethnic differences in EAT measurements, and the need for ethnic-specific cut points.

When linear regression was performed, after adjusting for age, gender, and diabetes, an increase in every unit of triglyceride level was associated with a sevenfold likelihood in the risk of developing the MetS, while an increase in every unit of EAT thickness was associated with an almost threefold likelihood of being diagnosed with MetS. It is known that excess adipose tissue, whether general or abdominal will give rise to elevated levels of nonesterified plasma fatty acids, which is a final product of triacylglycerol (triglyceride) hydrolysis. This overload of nonesterified fatty acids is thought to mediate adverse cellular effects like insulin resistance and has been found in patients undergoing weight loss interventions. However, our study has also shown that the triglyceride levels had highest discriminating capacity for the MetS and was associated with the highest odds in linear regression analysis.

So although EAT is most certainly associated with the MetS, and can identify individuals at increased cardiometabolic risk, it has a limited additional role compared to current risk markers. A recent study has demonstrated the utility of combining the BMI and waist circumference (wBMI) into a single index, which proved to be superior than BMI and waist circumference alone, for better-characterizing obesity regarding the cardiovascular risk. The wBMI marker is promising and will applied in this sample in a future study.

**Strengths and limitations**

To the authors’ knowledge, this is the first study in South Africa to determine the value of EAT in identifying individuals who may be at a high risk for the MetS. There was a large sample size when compared to other published works in this area. 2D echocardiography was used and therein lies the limitation since echocardiographic-derived epicardial fat thickness reflects a linear measurement at a single location. This may underestimate the amount of EAT that is actually there, since EAT is not uniformly distributed around the heart. The cross-sectional design of this study which evaluated the association between EAT and MS could not determine causality – further studies are needed to define the actual mechanisms to explain this association. EAT is known to have a role in the inflammatory milieu which underpins the development of DM and MetS – it would have been useful to correlate plasma inflammatory markers and inflammatory activity of EAT and their association with the presence of the MetS.

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**Conflicts of interest**

There are no conflicts of interest.

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**Table 4: Multivariate stepwise logistic regression analysis for metabolic syndrome**

|          | P     | OR   | 95% CI Lower | 95% CI Upper |
|----------|-------|------|--------------|--------------|
| Age      | 0.000*| 1.1  | 1.03         | 1.08         |
| Diabetes | 0.358 | 0.79 | 0.48         | 1.3          |
| BMI      | 0.918 | 1.0  | 0.94         | 1.08         |
| Waist circumference | 0.006*| 1.0  | 0.99         | 1.062        |
| Blood glucose | 0.000*| 1.2  | 1.09         | 1.3          |
| Total cholesterol | 0.27 | 1.3  | 0.82         | 2.0          |
| Triglycerides | 0.000*| 7.01 | 4.3          | 11.4         |
| HDL cholesterol | 0.000*| 4.02 | 2.05         | 0.04         |
| LDL      | 0.819 | 0.95 | 0.59         | 1.5          |
| LAVI     | 0.925 | 0.99 | 0.96         | 1.04         |
| RWT      | 0.886 | 0.79 | 0.034        | 18.7         |
| LV mass  | 0.37  | 1.00 | 0.97         | 1.01         |
| EAT      | 0.000*| 2.3  | 1.63         | 3.2          |

*P<0.001. OR=Odds ratio, CI=Confidence interval, BMI=Body mass index, HDL=High-density lipoprotein, LDL=Low-density lipoprotein, LAVI=Left atrial volume index, RWT=Relative wall thickness, LV=Left ventricular, EAT=Epicardial adipose tissue.
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