Epicardial Adipose Tissue Thickness and its Corelation with Metabolic Risk Parameters in People Living with HIV: A RIMS Study

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Abstract

Context: Epicardial fat envelopes the coronary vessel adventitia without fascial separation, thus pathologic inflammation in the fat may promote the growth of atherosclerotic plaque in coronary arteries in an 'outside-in' fashion. Epicardial fat is quantitatively increased in HIV compared to un-infected people. **Aims:** 1. To assess Epicardial Adipose tissue (EAT) by Computed tomography (CT) in PLHIV receiving first line ART (antiretroviral therapy) 2. To correlate EAT with metabolic risk parameters. **Material and Methods:** 215 HIV-infected patients aged >18 years on first line ART were included in the cross sectional study. EAT thickness were measured by CT scan. Metabolic parameters were measured based on metabolic syndrome criteria. **Statistical Analysis Used:** Data analysis was done using IBM SPSS version ver. 21. Probability value of less than 0.5 was taken as significant. **Ethical Issues:** The study was carried out after obtaining approval from the Institutional Ethical Committee (IEC), Regional Institute of Medical Sciences, Imphal. **Results:** Half of the patients were found to have EAT thickness of 8.1-9 mm and 12.6% of cases had EAT of >9 mm. Mean epicardial thickness was 8.3 mm ± 0.7 mm for whole population. Triglyceride and high density lipoprotein (HDL) were also found to have positive correlation with EAT thickness (r_p = 0.364, P = 0.04 and r_p = 0.343, P = 0.05 respectively). **Conclusion:** Epicardial adipose tissue thickness is increased in PLHIV receiving highly active anti retroviral therapy (HAART) and positively co-related with parameters of metabolic syndrome such as waist circumference, HDL cholesterol and triglyceride level.

Keywords: Epicardial adipose tissue, HAART, metabolic parameters, PLHIV, visceral adiposit

INTRODUCTION

Individuals infected with human immunodeficiency virus (HIV) are at increased risk of cardiometabolic complications. The pathophysiological basis for such a higher risk is complex; some could be related to HIV disease process and others could be related to treatment with antiretroviral drugs.[1] The use of antiretroviral therapy (ART) is accompanied by expanding or altered visceral fat depots, which are metabolically active and harbor an inflammatory milieu that contribute to insulin resistance and promotes atherosclerosis.[2]

Metabolic syndrome (MetS) includes visceral adiposity, which is closely associated with diabetes, dyslipidemia, hypertension, and cardiovascular disease. The relationship between waist circumference and intraabdominal obesity or visceral adipose tissue (VAT) depends on age, gender, and ethnicity.[3] Epicardial adipose tissue (EAT) is the fat located between the myocardium

and visceral pericardium [Figure 1].[4] Because EAT and VAT share the same embryological origin from the splanchnopleuric mesoderm, it is conceivable that EAT may be as strong a risk marker of cardiovascular disease as VAT.[5] Though EAT has been linked with incident cardiovascular events in the general population, there is paucity of studies that assess the role of EAT as a cardiometabolic risk marker in patients with HIV.

Aims and objectives

1. To assess EAT by computed tomography (CT) in PLHIV receiving first line ART
2. To corelate EAT with metabolic risk parameters.

Access this article online

Quick Response Code:

Website:
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DOI:
10.4103/ijem.IJEM_34_18

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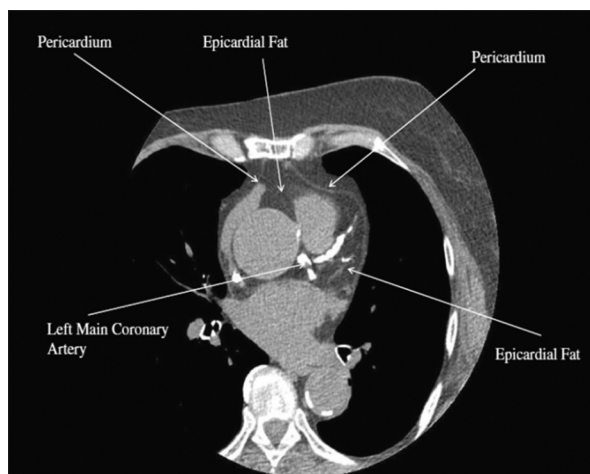E-mail: jayakeisham@gmail.com

Figure 1: Epicardial adipose tissue (EAT)

SUBJECTS AND METHODS

This cross-sectional study was conducted in 215 HIV-infected patients admitted to medicine ward or registered in ART center, Regional Institute of Medical Sciences (RIMS), Imphal, from October 2014 to September 2016.

Inclusion criteria: Both male and female patients of age >18 years on first line ART regime.

Exclusion criteria: Patients with history of smoking, diabetes, hypertension, cardiovascular diseases, BMI >29 kg/m², patient on stavudine or abacavir, statins, fibrates, and patients not willing to participate.

The patients were provided with written-informed consent. For all eligible participants a detailed history with emphasis on drug adherence, drug history, and duration on first-line therapy was taken and underwent thorough clinical examination, routine laboratory tests according to NACO guideline.

The quantification of EAT thickness was done using plain CT thorax by Brilliance 64, Phillips machine (64-slice multidetector CT). CT scan of the cardiac region extended from carina to inferior border of the heart. Thick slice (5-mm thick slices) axial images of the cardiac scan were analyzed for the epicardial fat, which have attenuation value of −30 to −200 Hounsfield units (HU). Using freehand ROI (region of interest tool) tool, the epicardial fat were outlined manually on the workstation and the surface area covered was recorded for each single thick slice axial images. Epicardial fat volume of each thick slice was calculated by multiplying the surface area of the epicardial fat by a factor of 5 mm. The epicardial fat volume of the thick slices was then summated to yield the total epicardial fat volume.

Anthropometric measurement was done by measuring height (centimeters) and weight (kilograms) with subject wearing light clothing and no shoes. BMI (kilogram per square meter) was calculated. Waist circumference was assessed at the midpoint between 12th rib and the iliac crest. Serum lipid profile (total cholesterol, high density and low-density

Table 1: Study characteristics

Characteristics	Values
Age	38.3±9.6 years
Male	75.8%
Females	24.2%
ART: TLE	71.2%
ART: ZLN	28.8%
ART duration	41.6% (1-5 years)
CD4 count >300 cells/cumm	70.6%
Mean EAT	8.3±0.7 mm
EAT above 50 years	8.7±1.1 mm ($P<0.05$)
BMI >23 kg/m²	30%
Waist circumference	M: 104.5±9.7 cm; F: 107.2±11.0 cm
FBS	86.71±33.42 mg/dl
HDL	Male: 36.2±8.3 mg/dl
	Female: 38.12±4.67 mg/dl
Triglyceride	191.36±101.17 mg/dl
BP	SBP: 124±10 mmHg; DBP: 74±12 mmHg

Table 2: Epicardial adipose tissue thickness corelation with metabolic risk factors

Variables	Pearson corelation	*P*
EAT thickness (mm)		
Male/female	$t=-7.312$	0.000***
BMI	$r_p=-0.076$	0.265
Waist circumference	$r_p=0.134$	0.01**
CD4 count	$r_p=-0.029$	0.672
Cholesterol	$r_p=-0.004$	0.952
Triglyceride	$r_p=0.364$	0.04*
HDL	$r_p=0.343$	0.05*
ART duration	$r_p=-0.076$	0.265
ART regime: TLE/ZLN	$t=2.731$	0.007**
Fasting blood glucose > 100 mg/dl	$r_p=-0.104$	0.126
BP >130/85 mmHg	$r_p=-0.096$	0.23

lipoproteins, and triglyceride) and fasting blood glucose levels were measured using standard techniques. CD4 cell counting was done by flow cytometry (FACS count).

The study was carried out only after obtaining approval from the Institutional Ethics Committee (IEC), Regional Institute of Medical Sciences.

Statistical analysis: Data analysis was done using IBM SPSS version ver. 21. Data were described using mean and percentages. Test of significance was done using chi square test, *t*-test, and ANOVA. Probability value of less than 0.5 was taken as significant.

RESULTS

Majority of the patients were from the age group 40–49 years. Mean age was 38.3 years with a standard deviation of 9.6 years. Three fourth of the respondents were males (75.8%) as compared to females (24.2%). Among 215 patients, 153 patients were taking TLE (71.2%) and 62 were taking

ZLN (28.8%). Majority of the patients had been on ART treatment for 1–5 years (41.6%) and maximum of the patients were found to have a CD4 count of more than 300 cells/cumm (70.6%).

Most of the patients had normal BMI (69.3%) in the range of 18.5–24.9 kg/m², 14.4% were overweight whereas 6.5% of patients fall in the obesity range (30 kg/m² or higher). Females had more number of overweight (47.4% vs 3.6%) and obesity (7.5% vs 7.3%) patients than males and the finding was statistically significant ($P < 0.05$). Abdominal waist circumference was significantly more in females than males (107.2 ± 11.0 cms vs 104.5 ± 9.7 cms, $P = 0.01$). We found that 6.2% of the patients were found to have fasting blood glucose above 100 mg/dl ($P = 0.126$, insignificant) and 6.6% of them have BP above 130/85 mmHg ($P = 0.23$, insignificant).

In our study, half of the patients were found to have EAT thickness of 8.1–9 mm. EAT thickness of >9 mm was found in 12.6% of cases. Mean epicardial thickness was 8.3 mm for whole population with a standard deviation of 0.7 mm. Patients with age above 50 years had increased EAT thickness than others age group (8.7 ± 1.1 mm). The finding was statistically significant ($P < 0.05$). Females had an increased EAT thickness compared to males in our study (8.9 ± 0.7 mm vs 8.1 ± 0.5 mm) [Tables 1 and 2].

However, our study found a negative corelation between EAT thickness and BMI ($r_p = –0.076$) and the finding was statistically insignificant ($P > 0.05$). With the increase in CD4 count there was increase in EAT thickness ($r_p = –0.029$) and vice versa and the finding was significant ($P < 0.05$). Triglyceride and HDL were also found to have positive corelation with EAT thickness ($r_p = 0.364$, $P = 0.04$ and $r_p = 0.343$, $P = 0.05$, respectively). There was a poor corelation between cholesterol level and EAT thickness ($r_p = 0.004$, $P = 0.952$). There was a negative corelation between duration of ART and EAT thickness ($P = 0.265$). Patient who were on ZLN had increased EAT thickness than patient on TLE (8.4 ± 0.9 vs 8.3 ± 0.6) but the finding was insignificant ($P = 0.1$).

Discussion

EAT and VAT share the same embryonic origin.[5] The adipose tissue releases adeponectins, a protein hormone involved in free fatty acids and glucose metabolism. Increased production of proinflammatory cytokines like cytokines-1, 6, TNFα, and resistin in obesity interfere with the production of novel adiponectin resulting in hyperinsulinemia and MetS.[6]

HIV infection as well as HAART increase deposition of adipose tissue in the abdomen and epicardium with simultaneous wasting of hip and thigh due to mixed lipodystrophy, which is more clearly observed in females than male. Longer the duration of ART (>5 years), more is the lipodystrophy. It is also corelated with the level of CD4 T-cells as T-lymphocytes are increased in the adipose tissue of obese PLHIV.[7] In our

study of 215 cases, majority of the respondents were from age group 40–49 years with a mean age of 38.3 years. Three by fourth of them were males as more number of males were registered during the study period (M: F = 1.3:1). More than half (TLE-71.2% vs ZLN-28.8%) of population were on TLE as per revised guidelines of NACO (2014). A total of 39.5% of them was on ART for more than 5 years with a CD4 count above 300 mm³ (70.6%) showing the effectiveness of HAART in immunomodulation, improvement of immunity, and prolongation of life expectancy.

Measurement of EAT thickness gave an increase in value in 50% (8.1–9 mm) and > 9 mm in 12.6%, rest (37.4%) had normal thickness (7.18 mm). Age above 50 years, population had thicker EAT ($P = 0.05$) compared to younger population. It can be explained by the fact that ageing process leads to decrease in lean body mass and increase in the visceral fat thereby producing more of metabolic changes. With the increase of CD4 T-cell count, there was increase in EAT thickness and vice versa ($P = 0.05$). A study by Brener Malso found the association between current CD4 T-cell count and cumulative exposure to HAART with EAT.[8] Mariana Diaz-Zamudio stated that increased EAT thickness among HIV-infected cases are related to duration of HIV infection and HAART exposure. They found that presence of clinical lipoaccumulation is secondary to HAART and not due to chronologic age of the patient.[7] The direct ART toxicity, which is the result of metabolic alterations induced by these therapies, and/or the potential pathological effects of immune-reconstitution may express itself as EAT. T-lymphocytes are increased in the adipose tissue following HIV infection and ART treatment. These reconstituted CD4 lymphocytes may behave in a proinflammatory and proatherogenic way rather than being solely protective.[9] In our study, patients receiving ZLN were found to have higher value of EAT that is in conformity with study by Brenner *et al*.[8]

The result of mean EAT in males was 8.1 ± 0.5 mm and in females 8.9 ± 0.7 mm in our study that is contradicted to the finding by Guaraldi *et al.* and Iacobellis *et al.* and in conformity with Torriani *et al*.[5,10,11] According to Torriani *et al.*, HIV-infected females are associated with more frequency of fat redistribution and metabolic abnormalities leading to increased fat accumulation in EAT and visceral fat.[11] In our study, females had more number of overweight (47.4% vs 3.6%) and obesity (7.5% vs 7.3%) compared to males and the finding was statistically significant ($P = 0.05$). There was a negative corelation between EAT and BMI ($P = 0.265$) that is in contrast with Brenner M *et al.* and in conformity with Lo *et al.* that can be explained by late initiation of HAART (NACO guideline) in our population as compared to western countries producing earlier and higher degree of lipodystrophy and also may be as a result of malnutrition seen commonly in these group of population.[8,12]

Abdominal waist circumference was significantly more in females than males (107.2 ± 11 vs 104.5 ± 9.7) having a

P value of 0.01. According to our study, there was HIV-related dyslipidemia with elevated triglyceride with decreased HDL, which is in conformity to the study done by Riddler *et al*.[13] We did not find association of EAT with blood glucose and blood pressure in our population. In our study, 6.2% of the patients were found to have fasting blood glucose above 100 mg/dl (*P* = 0.126, insignificant) and 6.6% of them had BP above 130/85 mmHg (*P* = 0.23, insignificant). This could mean that our population are less prone to alterations in glucose metabolism and hypertension compared to the western population.

Conclusion

EAT thickness is increased in PLHIV receiving HAART (first line). EAT is positively corelated with parameters of MetS such as waist circumference, HDL cholesterol, and triglyceride level. Thus, EAT measurement among HIV cases can be considered as a reliable method of assessing cardiovascular risk among patients receiving HAART.

Limitations

This is a single center-based cross-sectional study, thus we are able to establish only the association of EAT and HAART. Shorter duration of follow-up might be affected by the survival bias. We might be missing considerable number of patients died before the initiation of our study who might have significant EAT thickness. Community-based cohort study including controls from general population for comparison will give a better result.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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