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Human epicardial lipid profile status in CAD patients: Correlation with age, diabetes and hypertension

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ABSTRACT

The role of obesity is well established in the pathogenesis of Coronary Artery Disease (CAD) and is found to be related to adipocytes. For more than two decades, the role of epicardial fat remains controversial and debatable. Hence, we analyzed the lipid profile status of human epicardial and subcutaneous fat in CAD patients based on risk factors and age. We have found that epicardial fat composition is independent of age and epicardial fat may exert a protective mechanism in atherosclerotic process through elevated levels of HDL and phospholipids than subcutaneous fat.

KEYWORDS

Epicardial;
Subcutaneous;
Lipid;
Coronary artery disease;
Diabetes;
Hypertension.

INTRODUCTION

Studies across the regions have clearly demonstrated the role of abnormal levels of lipid profile with pathogenesis of atherosclerosis in Coronary Artery Disease (CAD) patients [1,2] and obesity[3]. The importance of obesity in the prediction of cardiovascular disease is also well known and is considered as the main risk factor for CAD. Several studies have documented that obesity related disorders activate monocytes which will trigger atherosclerosis which in turn causes CAD[4]. Adipose tissue, not only stores fat but also acts as an active endocrine organ that secretes various types of bioactive molecules called adipokines. These substances include leptin, adiponectin, resistin, apelin, and TNF-alpha, IL-6, visfatin, vaspin and plasminogen activator-I[5]. Circulating levels of these proinflammatory cytokines are increased significantly in obese people, who have increased accumulation of visceral fat[6]. Visceral fat has different biological characteristics when compared to subcutaneous fat and thus plays a vital role in the development of CAD.

Epicardial fat (EF), which is a true visceral fat on the cardiac myocardium evolves from the brown adipose tissue during embryogenesis. It occupies 80% of the cardiac outer surface and constitutes 20% of total heart weight. Since EF is located proximally to the adventitia of the coronary arteries as well its direct interaction with myocardium, might involve significant role in the pathogenesis of CAD[7]. Mature adipocytes are located in the epicardial fat especially anterior to the right ventricle (RV) and these may act as more readily available, direct sources of free fatty acid for cardiomyocytes[8]. EF is also clinically related to LV mass and other features of the metabolic syndrome, such as concentrations of LDL cholesterol, fasting insulin and adiponectin and arterial blood pressure[9].

Subcutaneous fat (SF) is the adipose tissue placed directly under the skin layers which contain fatty tissues and blood vessels that nourishes the skin and nerves[10]. Therefore, the present study was conducted to investigate the lipid profile status of epicardial and subcutaneous adipose tissue in CAD patients based on the presence and the absence of cardiovascular risk factors such as age, diabetes mellitus, and hypertension which might provide the initial real identification of EF role in CAD process.

MATERIALS AND METHODS

Institutional Ethical clearance was obtained for the proposed study. The samples were collected from ten CAD patients who underwent elective Coronary Artery Bypass Grafting (CABG) surgery in our institute after their obtaining the patients informed consent. Epicardial and subcutaneous adipose tissues samples were obtained from near the proximal right artery and site of saphenous vein harvesting in the leg respectively. The samples were maintained at -80 degree Celsius.

The lipids were extracted from tissue using Folch's method[11]. For lipid analysis, homogenized tissue sample extract was prepared by mixing known volume of tissue with 10 ml of chloroform – methanol (2:1). Lipid profile assay such as total cholesterol[12], phospholipids[13], free fatty acids[14], triglycerides[15], and HDL (High Density Lipoproteins) and LDL (Low Density Lipoproteins) were analyzed in EF and SF tissue samples using standard procedures[16]. The subjects were characterized into groups based on the presence of risk factors (Diabetes (DM) and Hypertension (HTN)) and age. SPSS software version 16.0 was used for statistical analysis and 'p' value of less than 0.05 was considered statistically significant.

RESULTS

The demographic and clinical characteristics of individual patient were retrieved from medical records and are represented in TABLE 1. Most patients are about 52 years old with overweight and bordering obesity. Lipid profile study was performed to analyze the lipid status of EF and SF (Figures 1 and 2). The contents of all lipids except for HDL and phospholipids, were significantly higher ($p>0.05$) in SF than EF Based on patients age, study population were distributed with age below and above 60 yrs.

TABLE 1 : Study population demographic data.

Parameters	Subjects
Age (yr)	51.65± 13.5
Body weight (kg)	74.0 ±15.5
BSA (m^2)	1.80 ±0.30
BMI (kg /m^2)	27.0 ±3.00
Height (cm)	165.1 ±15.0

The lipid profiles of both EF and SF with patients below 60 years (Figure 3a and 3b) and above 60 years (Figure 4a and 4b) of age were analyzed. Irrespective of age, all lipid levels were

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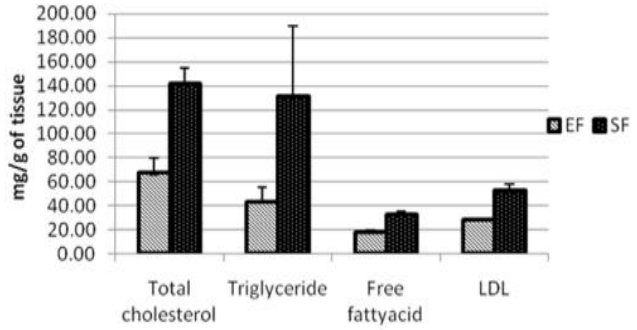

Figure 1: Estimation of the total cholesterol, triglyceride, free fatty acid and LDL levels in epicarddial and subcutaneous fat.

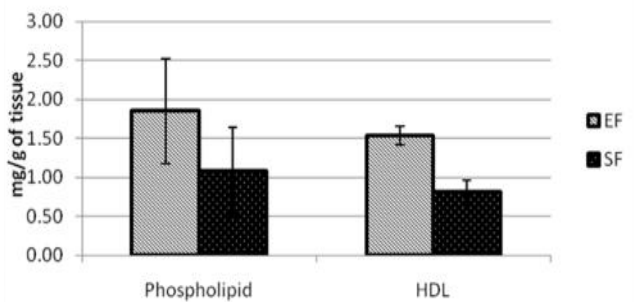

Figure 2: Estimation of phospholipid and HDL in epicardial and subcutaneous fat.

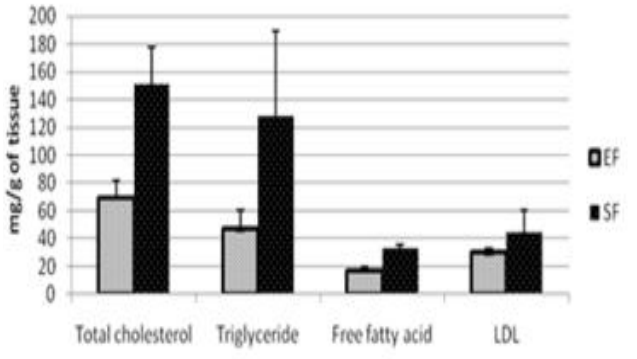

Figure 3a: Estimation of total cholesterol, triglyceride, LDL and free fatty acid in patients below 60 years of age in epicardial and subcutaneous fat.

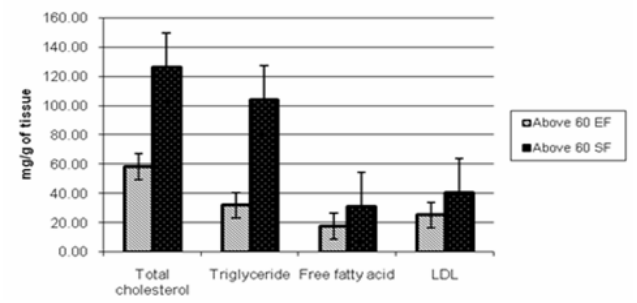

Figure 4a : Estimation of total cholesterol, triglyceride, LDL and free fatty acid in patients above 60 years of age in epicardial and subcutaneous fat.

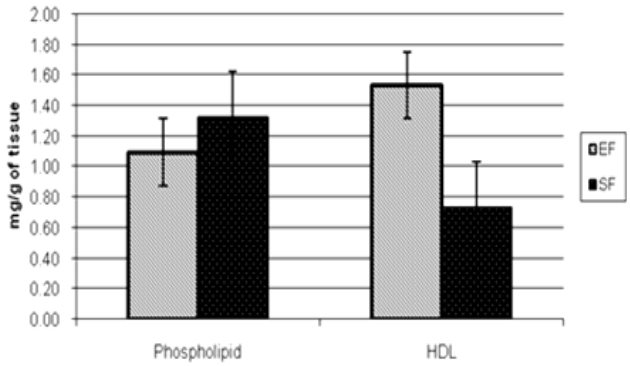

Figure 4b : Phospholipid and HDL estimation in patients above 60 years of age in epicardial and subcutaneous fat.

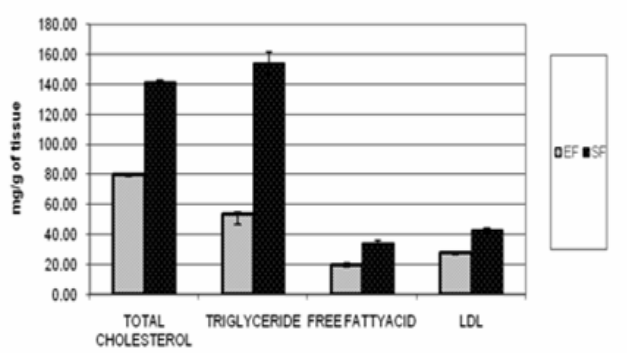

Figure 5a : Estimation of total cholesterol, triglyceride, LDL and free fatty acid in patients with Diabetes Mellitus in epicardial and subcutaneous fat.

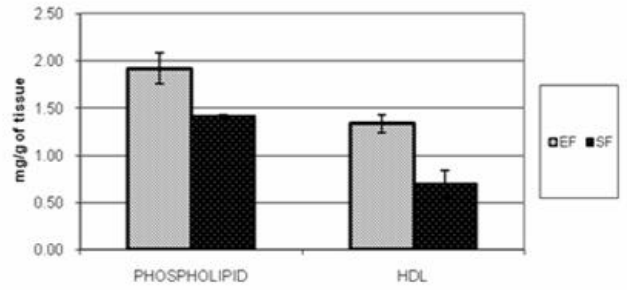

Figure 5b: Phospholipid and HDL estimation in patients with diabetes mellitus in epicardial and subcutaneous fat.

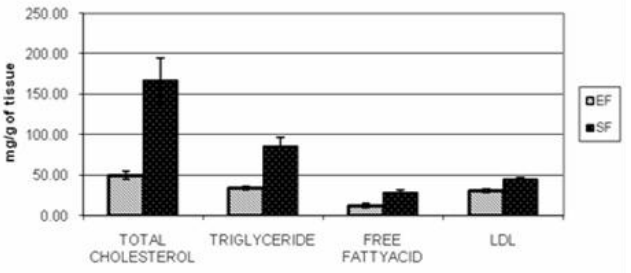

Figure 6a : Estimation of total cholesterol, triglyceride, LDL and free fatty acid in patients without Diabetes Mellitus in epicardial and subcutaneous fat.

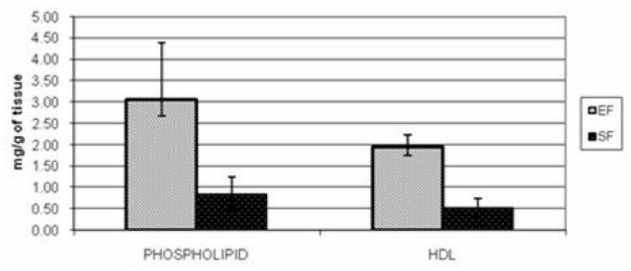

Figure 6b: Phospholipid and HDL estimation in patients without Diabetes Mellitus in epicardial and subcutaneous fat.

high in SF except for HDL and phospholipids than EF ($p<0.05$).

The diabetic (Figure 5a, 5b) and non diabetic (Figure 6a, 6b) CAD patients lipid profiles were estimated and their lipid contents were generally high in SF and low in EF, except for HDL and phospholipids values. However, in patients without diabetes, phospholipids and HDL levels were exceptionally higher in EF than SF, resulting in a greater difference between EF and SF than in patients with diabetes.

The lipid profiles were performed between hypertensive (Figure 7a, 7b) and non hypertensive patients (Figure 8a and 8b) showed similar pattern of previous result. In both groups, all lipid levels were low in EF except for HDL and phospholipids levels. Similar to the diabetic and non diabetic group, in patients without hypertension, phospholipid and HDL levels were significantly higher in EF than SF, in patients with hypertension.

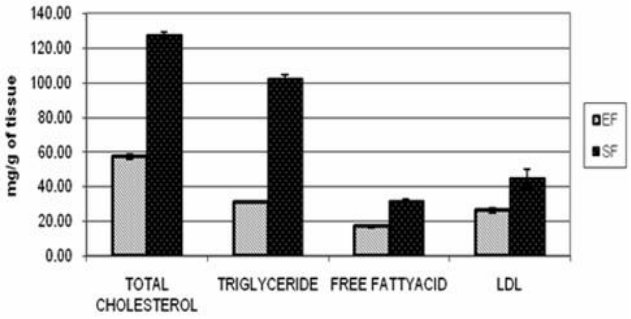

Figure 7a : Estimation of total cholesterol, triglyceride, LDL and free fatty acid in patients with hypertension in epicardial and subcutaneous fat.

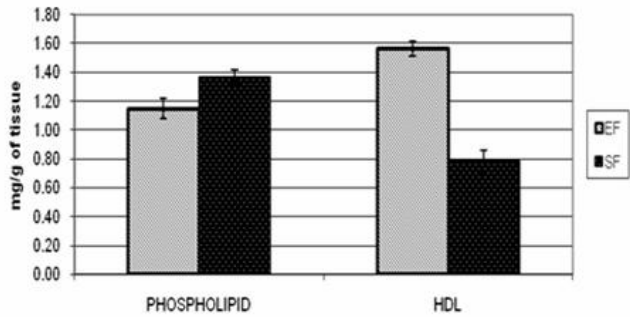

Figure 7b : Phospholipid and HDL estimation in patients with hypertension in epicardial and subcutaneous fat.

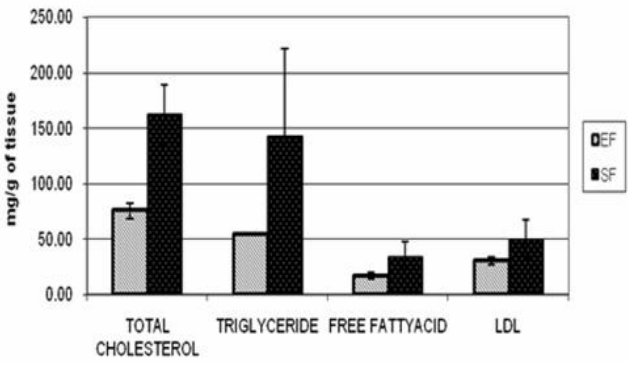

Figure 8a : Estimation of total cholesterol, triglyceride, LDL and free fatty acid in patients without hypertension in epicardial and subcutaneous fat.

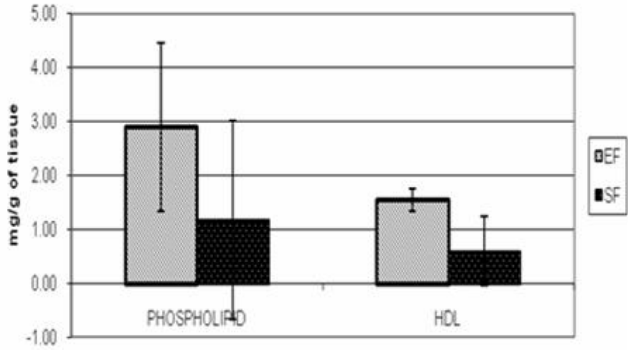

Figure 8b : Phospholipid and HDL estimation in patients without hypertension in epicardial and subcutaneous fat

DISCUSSION

In order to investigate the potential effects of epicardial fat in CAD patients, experiments were conducted to determine the lipid content variation between EF and SF. Patient's results have shown that EF contains low levels of total cholesterol, triglyceride, LDL and free fatty acid. High levels

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of HDL and phospholipids were observed in EF. These results were in converse to SF. Previous literatures have demonstrated the composition of fatty acid in epicardial and subcutaneous adipose tissue[17] but this is the first report which gives deep insight of lipid content and provides us the option of considering that EF may exert protective mechanism.

In our study, patients above or below 60 years did not show significant variation in the lipid composition between EF and SF in similar to previous study that variation in EF content is not generally associated with age[18]. An autopsy study assessed the relationship between EF extent, fat distribution and CAD lesion using cardiac computerized tomography and concluded that EF is correlated positively with CAD staging and also independent of age in supporting our data[19]. Our study supports the generalization that variation in age does not affect lipid composition in epicardial and subcutaneous tissue.Between diabetic and non diabetic status, we observed that diabetic patients had lower total cholesterol, triglyceride, fatty acid and LDL than subcutaneous, but higher phospholipids and HDL in epicardial fat. Non Diabetic patients had significantly higher value of HDL and phospholipid in epicardial than subcutaneous fat. Low HDL-C is characteristic in patients with type 2 diabetes, and our data supports that HDL level is lower in diabetic patients than in non diabetic. The lipid composition of adipose tissue is dependent on various factors like nutrition, metabolism, and storage[20]. Our data also suggests that epicardial fat has a significantly lower amount of HDL in diabetic than in non diabetic patients indicating that epicardial fat may be responsible of positive effects[21].

With our studies involving hypertension, hypertensive patients have higher amount of total cholesterol, triglycerides, fatty acid and LDL in subcutaneous fat but relatively lower levels of phospholipids and HDL. However, the levels of phospholipids and HDL were not significantly lower, ($p>0.001$), therefore lipid contents in epicardial and subcutaneous fat do not differ significantly between patients with and without hypertension. Fat distribution was found to be independently related with hypertension similarly to the previous study[22].

In conclusion, we found that EF might exert a protective mechanism to the cardiac myocardium by delaying the pathogenesis of atherosclerosis. Higher levels of HDL and phospholipids in EF are the main findings, which prompt us to think about its cardio-protective mechanism. Free fatty acids levels determined between EF and SF studies revealed that stored fatty acids may have an impact on the in metabolic function of adipocytes. To the best of our knowledge this is the first study that determined the lipid composition of epicardial and subcutaneous tissue and also its correlation with CAD risk factor and patient's age. However we have compared the epicardial adipose tissue with subcutaneous tissue from the leg region and it is not known whether such changes can occur in other fatty depots. Also, we have yet to determine the correlation of epicardial fat lipid composition and coronary artery disease. Therefore further research has to be conducted in patients with CAD to understand the exact mechanism by which EF exerts it protective mechanism.

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