INTRODUCTION

Visceral adiposity has been increasingly recognized as a marker for cardiovascular risk and metabolic syndrome, including glucose intolerance, hypertension, dyslipidemia, hyperinsulinemia, and atherosclerosis. The pathophysiology may be explained by its action as an endocrine and paracrine organ with various biological and metabolic functions, including a reservoir for several atherogenic inflammatory cytokines ***(Das, 2001).***

Visceral adipose tissue expresses numerous genes for secretory proteins, and several biologically active molecules secreted from adipose tissue (adipocytokines) may have important roles in the development of atherosclerotic diseases ***(Funahashi et al., 1999).***

Epicardial adipose tissue (EAT) is a particular form of visceral adipose tissue deposited around the heart and found in considerable quantities around subepicardial coronary arteries.

EAT shares a common embryological origin with abdominal adipose tissue. additionally, EAT of patients with significant coronary artery disease (CAD) has been shown to be a source of several inflammatory mediators and exhibited significant inflammatory responses, independant of body mass index (BMI) or diabetes ***(Mazurek et al., 2003).***

Earlier studies in cadavers showed that the weight of dissected epicardial fat is correlated with the heart weight, and that coronary atherosclerotic plaque tend to be more prominent on the arterial side in contact with EAT deposits.

Other studies have shown that EAT supplies free fatty acids for myocardial energy production and synthesis cytokines. Data from animal studies suggested that the rate of fatty acid synthesis is significantly greater in EAT than in any other depots of the body ***(Marchington et al., 1989; Marchington et al., 1990)***.

EAT measured either on the right ventricle or the amount surrounding the whole heart is significantly related to waist circumference, diastolic blood pressure, left ventricular mass, high level of insulin, and the severity of CAD assessed by coronary angiography ***(Iacobellis et al., 2003; Iacobellis et al., 2005).***

All these findings suggest that EAT plays a role in the development of coronary atherosclerosis via the association with conventional risk factors and also direct endocrine and paracrine effects. This hypothesis was suspected many years ago based on studies demonstrating the absence of atherosclerosis in human intramyocardial, but not epicardial, coronary arteries ***(Geiringer et al., 1951; Robicsek et al., 1994)***.

Segments of coronary arteries lacking EAT or separated from it by a bridge of myocardial tissue appear to be protected against the development of atherosclerosis. This may be due to the absence of adipose tissue in the myocardium as compared with epicardial coronary arteries ***(Chaldakov et al., 2001).***

de Vos et al. evaluated the relationship between peri-coronary EAT and cardiovascular risk factors and coronary artery calcification in 573 healthy post-menopausal women selected from participants in the PROSPECT study ***(de Vos et al., 2008).***

The wide range of using the Multi-slice computed tomography (MSCT) in diagnosis of atherosclerotic cardiovascular diseases raise the need for another simple techniques that add diagnostic tool to other risk factors without additional coast and during the same CT examination.

AIM OF THE WORK

To find the relation between peri-coronary epicardial adipose tissue and cardiovascular risk factors together with coronary artery calcification and atherosclerosis in post-menopausal women using the multi-detector CT.

EPICARDIAL ADIPOSE TISSUE GENERAL OVERVIEW

A growing amount of evidence suggests that regional fat distribution plays an important role in the development of an unfavorable metabolic and cardiovascular risk profile.

Epicardial fat is a metabolically active organ that generates various bioactive molecules, which might significantly affect cardiac function. This small, visceral fat depot is now recognized as a rich source of free fatty acids and a number of bioactive molecules, such as adiponectin, resistin, and inflammatory cytokines, which could affect the coronary artery response ***(Alexopoulos et al., 2010)***.

Furthermore, epicardial adipose mass might reflect intra-abdominal visceral fat. Therefore, we propose that MDCT assessment of this tissue could serve as a reliable marker of visceral adiposity.

Epicardial adipose tissue is also clinically related to left ventricular mass and other features of the metabolic syndrome, such as concentrations of LDL cholesterol, fasting insulin and adiponectin, and arterial blood pressure.

Erdogan et al. ***(Erdogan et al., 2012)*** postulated that coronary slow flow phenomenon may be related to the amount of epicardial adipose tissue measured in transthoracic echocardiography.

On the other hand, a large analysis of the Framingham population of 5200 patients confirmed that the amount of epicardial adipose tissue correlates with visceral, thoracic, abdominal adipose tissue, left ventricular mass, and the size of the left atrium ***(Fox et al., 2009)***.

Perivascular adipose tissue (PVAT) was previously evaluated in patients with myocardial infarction. It was recorded that its thickness was doubled compared to healthy volunteers.

In addition, PVAT thickness correlated to patient's age, body mass index (BMI), serum glucose and triglycerides, and mixed troponin I concentration. PVAT thickness surrounding the left anterior descending artery (LAD) positively correlated to vessel stenosis (quantitative coronary analysis) ***(Mazurek et al., 2008).***

It has been postulated that the quality rather than the quantity of peri-vascular tissue is a key factor for atherosclerosis ***(Yudkin et al., 2005)***.

However, other investigators have suggested that for the clinical importance of PVAT, its pro-inflammatory potential should be evaluated ***(Mazurek, 2009).***

MDCT assessment of epicardial fat could be a simple and practical tool for cardiovascular risk stratification in clinical practice and research.

In this section, we briefly review the rapidly emerging evidence pointing to a specific role of epicardial adipose tissue both as a cardiac risk marker and as a potentially active player in the development of cardiac pathology.

Thus, the increased accumulation of visceral fat is now widely seen as a defining characteristic of the so-called metabolic syndrome ***(Grundy et al., 2004; Carr et al., 2004).***

The recognition that adipose tissue is a highly complex endocrine organ that generates various molecules with profound local and systemic effects has spawned a remarkable interest in adipose tissue research ***(Sharma et al., 2002; Kershaw et al., 2004)***.

While much of the interest has focused on the importance of intra-abdominal visceral fat, some extra-abdominal visceral fat depots, including mediastinal and epicardial fat, have also been studied ***(Sharma et al., 2004)***

The last decade has witnessed a renewed interest in heart adiposity, especially as the result of the rapid development in the field of non invasive imaging, which has made it possible to quantify ectopic fat masses and contents with increasing level of accuracy.

The layers surrounding the heart include intra- and extra-pericardial fat. Their thickness and volumes can be quantified by echocardiography and computed tomography or magnetic

resonance imaging ***(Taguchi et al., 2001; Gorter et al., 2008; Iacobellis et al., 2009).***

Intrapericardial fat is in direct contact with the surface of the myocardium and the coronary vessels, with no separation by a physical fascia. Thus, the diffusion of secreted molecules and the migration of cells between these adjacent structures may occur.

This adherent fat layer has been defined as epicardial (between myocardium and visceral pericardium), whereas the term pericardial fat has been variably used to identify fat between myocardium and pericardium, which may include adipose tissue in the space between visceral and parietal pericardium, or just external but attached to the parietal pericardium, Peri-vascular fat surrounds arteries and arterioles.

The epicardial fat layer originates embryologically from mesothelial cells migrating from the septum transversum and hence obtains its vascular supply from the coronary arteries.

The extent of vessel wall or plaque calcification has been used as an additional index of severity of disease. In subjects free from clinical CAD, pericardial fat was independently associated with vascular calcification ***(Rosito et al., 2008; Ding et al., 2008; Sarin et al., 2008)***, in healthy postmenopausal women ***(de Vos et al., 2008)*** pericoronary fat thickness was related to calcification in respective coronaries. Instead, in patients with CAD the relationship was not progressive

(Djaberi et al., 2008) or was found only in subjects with normal BMI ***(Gorter et al., 2008)***

Epicardial Adipose Tissue: Anatomic, Biochemical & Functional Characteristics

The perception of adipose tissue (AT) has changed considerably over the last decades with the dramatic increase in the incidence of obesity and obesity-related co- morbidities. AT is a loose association of lipid-filled cells called adipocytes, which are held in a framework of collagen fibers. In addition to adipocytes, AT contains stromal–vascular cells, including fibroblastic connective tissue cells, leukocytes, macrophages, and preadipocytes (that are not yet filled with lipid), which contribute to structural integrity and constitute around 50% of its total cellular content ***(Kershaw et al., 2004).***

AT is increasingly recognized as a vital complex endocrine organ which generates various bio-active molecules with profound local and systemic effects ***(Kershaw et al., 2004)***. Although numerous population-based studies have shown a clear relationship between body mass index (BMI) "the most common index of adiposity used in clinical practice" and the documented co-morbidities associated with excess body fatness ***(Stamler et al., 1978; Manson et al., 1995; Cornier et al., 2011)***, obesity has remained a puzzling condition for clinicians because of its remarkable heterogeneity ***(Hassan et al., 2012)***.

The regional distribution rather than the absolute weight burden of AT plays an important role in the development of

metabolic and cardiovascular (CV) diseases. Peripheral subcutaneous adiposity exhibits an independent anti-atherogenic effect ***(Tanko et al., 2003)***, whereas accumulation of visceral adipose tissue (VAT) associates with increased prevalence of insulin resistance (IR), metabolic syndrome, and related CV complications ***(Lemieux et al., 1996).***

Epicardial adipose tissue (EAT) is a particular form of VAT deposited around the heart and found in considerable quantities around sub-epicardial coronary arteries. There is a growing evidence suggesting the physiological and metabolic importance of EAT, especially in the association of metabolic and CV risk profiles and the pathogenesis of atherosclerotic coronary artery disease (CAD) ***(Iacobellis et al., 2005; Iacobellis et al., 2007; de Vos et al., 2008; Alexopoulos et al., 2010).***

Anatomic Characteristics of Epicardial Adipose Tissue

The concept of cardiac adiposity, as a new CV risk factor and marker is rapidly emerging ***(Iacobellis et al., 2009; McGavock et al., 2010).*** The heart is covered by more or less abundant AT, particularly on its right side. EAT is the true visceral fat depot of the heart ***(Iacobellis et al., 2005; Sacks et al., 2007)***. It is located between the myocardium and visceral pericardium around both ventricles of the heart, with variable extent and distribution patterns ***(Iacobellis et al., 2005; Iacobellis et al., 2009).***

EAT is commonly found in the atrioventricular and interventricular grooves and along the major epicardial coronary arteries ***(Iacobellis et al., 2005).*** Minor foci of fat are located subepicardially along the free walls of the atria, the ventricles and around the two appendages. As the amount of epicardial fat increases, it progressively fills the space between the ventricles, sometimes covering the entire epicardial surface ***(Iacobellis et al., 2009).*** Interestingly, a small amount of AT extends from the epicardial surface into the myocardium, often following the adventitia of the coronary artery branches. Overall, there appears to be a close functional and anatomic relationship between the EAT and myocardium of the heart. Both share the same microcirculation, with no fascia (as found on skeletal muscle) separating the adipose and myocardial layers ***(Iacobellis et al., 2005)***.

Whereas generalized and abdominal adiposity clearly increase with aging, there have been some controversies whether epicardial adiposity also does so. *Silaghi et al* demonstrated a strong positive correlation between age and all EAT measurements over the entire age spectrum in adults ***(Silaghi et al., 2008)***, which was supported previously by some autopsy examinations ***(Schejbal, 1989)*** and MDCT studies ***(de Vos et al., 2008; Sanjay et al., 2008)***. In contrast, some echocardiographic studies did not find any relationship between age and EAT ***(Iacobellis et al., 2003; Corradi et al., 2004)***.

EAT thickness may differ also according to gender and ethnicity. In a Japanese study ***(Jeong et al., 2007)***, the mean echocardiographic EAT thickness was 6.3 mm, while in a Korean study ***(Ahn et al., 2008)*** it was 3.2 mm. In USA studies, median values of EAT thickness were extremely variable; it was 9.5 mm in men and 7.5 mm in women in one study ***(Iacobellis et al., 2008)***, while another study ***(Chaowalit et al., 2006)*** reported a median value of 2.2 mm. Iacobellis et al and Fluchter et al pointed out that EAT is thicker in men than in women ***(Iacobellis et al., 2008; Fluchter et al., 2007)***, however *Ahn et al* did not find any gender difference in EAT thickness ***(Ahn et al., 2008)***.

Biochemical & Functional Properties of epicardial adipose tissue:

A dichotomous role, both unfavorable and protective, has been attributed to EAT ***(Iacobellis et al., 2011).*** **Table 1,** but its physiology is not completely clear. EAT may play a role in coronary artery mechanical buffering against arterial wave torsion, coronary artery vasomotion and remodeling, as well as protection of the cardiac and coronary autonomic nerve supply ***(Sacks, 2009)***. Mitochondrial brown fat uncoupling protein 1 (UCP1) expression was found to be higher in human EAT than in other AT deposits, which suggests that EAT might function in the same way as brown AT to defend the myocardium and coronary arteries against hypothermia ***(Sacks et al., 2009)***.

Furthermore, EAT has a smaller adipocyte size but higher rates of fatty acid uptake, secretion, and breakdown in response to catecholamines than other visceral fat depots ***(Marchington et al., 1990)***. The high lipolysis observed in EAT might be due to several factors. The reduced antilipolytic effect of insulin in VAT and the increased activity of β-adrenergic receptors, especially β3 receptors, could be evoked as possible mechanisms.

Based on approximately 2-fold higher rates of lipolysis and lipogenesis in guinea pig epicardial fat than other fat depots, Marchington et al proposed that EAT serves to capture and store intravascular free fatty acid (FFA) to protect cardiomyocytes from exposure to excessive coronary arterial FFA concentrations during increased energy intake ***(Marchungton et al., 1989; Marchington et al., 1990)***. Thus, increased EAT could scavenge excess fatty acids, which interfere with the generation and propagation of the contractile cycle of the heart, causing ventricular arrhythmias and alterations in repolarization ***(Paolisso et al., 1997; Manzella et al., 2002)***.

On the other hand, the high lipolytic activity of EAT suggests that this tissue might also serve as a ready source of FFA, channeling FFA to the myocardium to meet increased myocardial energy demands, especially under ischemic conditions.

FFA kinetic studies showed that under normal basal conditions, endogenous FFAs are released into the coronary veins and then into the coronary venous sinus ***(Wisneski et al., 1987; Nelson et al., 2007)***.

The source for this FFA is thought to be EAT lipolysis ***(Nelson et al., 1987)***, since other possibilities such as hydrolysis of intracardiomyocyte triglyceride or hydrolysis of circulating very-low-density-lipoprotein (VLDL) triglyceride in coronary blood seems unlikely ***(Wisneski et al., 1987; Sacks et al., 2007)***.

The reason for FFA efflux into coronary venous blood is unclear. It might represent an "overflow" of FFAs not used by the myocardium. Alternatively, it might be a direct source of FFAs for the pulmonary arterial circulation, since vasoactive prostanoids are generated by the pulmonary arterial endothelium from FFA precursors ***(Baber et al., 2005; Sacks et al., 2007)***.

The fact that coronary sinus FFA accounts for a minor fraction of systemic FFA flux ***(Nelson et al., 2007)*** supports the hypothesis that EAT functions as a local myocardium-specific triglyceride depot.

Table (1): Known or Attributed Physiological and Pathophysiological Functions of EAT
(Iacobellis et al., 2011)

Physiological	Pathophysiological
Known	***Known***
• Energy source to the myocardium	• Excess free fatty acid synthesis and release
• Source of anti-atherogenic and anti-inflammatory adipokines	• Modulation of intra-myocardial fat content
• Mechanical protection of the coronary artery	• Intrinsic inflammatory status
	• Source and secretion of proatherogenic and proinflammatory adipokines
	• Correlation with coronary artery disease
	• Mechanical relations with bi-ventricular hypertrophy
	• Mechanical relations with impaired bi-ventricular diastolic relaxation and filling
	• Correlation with atrial fibrillation
Attributed	***Attributed***
• Protection of the myocardium against the toxicity of excess free fatty acids	• Functional relationship with the heart
• Coronary artery positive remodeling	• Causal and independent role in coronary artery disease
• Thermoregulation of the myocardium	• Causal and independent role in atrial fibrillation
• Properties as cold-activated brown fat	• Abnormal regulation of intrinsic cardiac nervous system
• Regulation of the intrinsic cardiac nervous system	