Relationship Between Peri-coronary Epicardial Adipose Tissue Volume and Coronary Atherosclerotic Burden

A Thesis Submitted for Partial Fulfillment of Doctorate Degree of Cardiovascular Medicine

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Abstract:

Background Epicardial adipose tissue (EAT) is a complex endocrine organ that express a variety of inflammatory mediators which may contribute to the pathogenesis of coronary artery disease (CAD). Resistin is a novel adipokine that has been linked to inflammation and atherosclerosis. No data exist regarding the relation between serum resistin, EAT volume, and CAD.

Purpose To investigate the relation between serum resistin, EAT volume and coronary atherosclerotic burden.

Methods The study recruited 32 male patients with stable angina pectoris and angiographic evidence of significant (≥ 50%) coronary stenosis (median age: 54 y, body mass index "BMI" 28 kg/m^2, 14 diabetes, 20 hypertension, 19 smoking). Eleven age-matched healthy male volunteers served as control group. All patients were not on statins. EAT volume indexed to body surface area (EAT-i volume) was quantified by cardiac magnetic resonance (CMR). Coronary artery calcium (CAC) score and plaque volume were measured by multidetector computed tomography. Serum levels of lipoproteins, adiponectin, leptin, and resistin were measured.

Results Both groups were similar in terms of BMI, waist hip ratio, and serum lipoproteins levels. EAT-i volume (57.1 vs. 24.5 cm^3/m^2, $p<0.001$) and serum resistin (7.5 vs. 6.0 ng/ml, $p=0.017$) were significantly higher in CAD patients than control group. EAT-i volume showed significant positive linear correlations with serum resistin ($r=0.69$, $p<0.001$), CAC score ($r=0.51$, $p=0.003$), and coronary plaque volume ($r=0.45$, $p=0.01$) in CAD patients. Serum resistin showed significant positive linear correlation with CAC score ($r=0.37$, $p=0.05$). In CAD patients, EAT-i volume was significantly increased among resistin tertiles (66.2 vs. 58.2 vs. 38.5, $p=0.001$). No significant correlations were detected between EAT-i volume and serum adiponectin as well as leptin levels. In a multivariate regression analysis, EAT-i volume was the most powerful predictor of CAC score compared to other conventional risk factors for CAD [exp(B)=12.0, 95% CI=4.9 – 19.1, $p=0.002$]. Serum resistin was independent predictor of increased EAT-i volume [exp(B)= 3.16, 95% CI=1.35 – 4.98, $p=0.001$].

Conclusions Epicardial adipose tissue volume is independently associated with coronary atherosclerotic burden in stable coronary artery disease patients. Resistin may provide a possible mechanistic link between epicardial adipose tissue and coronary atherosclerosis

Key word:CAD-EAT- Peri-coronary- ACS-ECG

Table of Contents

Table of Tables

Table of Figures

Abbreviations & Acronyms

ACS: Acute coronary syndrome

AF: Atrial fibrillation

ALT: Alanine transaminase

AST: Aspartate transaminase

AT: Adipose tissue

BP: Blood pressure

BMI: Body mass index

BSA: Body surface area

CABG: Coronary artery bypass grafting

CAC: Coronary artery calcium

CAD: Coronary artery disease

CCSC: Canadian cardiovascular society class

CCTA: Coronary computed tomography angiography

CHF: Congestive heart failure

CIMT: Carotid intima media thickness

CMR: Cardiac magnetic resonance

CTO: Chronic total occlusion

CV: Cardiovascular

EAT: Epicardial adipose tissue

EAT-i: Epicardial adipose tissue indexed to body surface area

ECG: Electrocardiogram

ELISA: Enzyme linked immune sorbent assay

FDA: Food and drug administration

FFA: Free fatty acids

HOMA-IR: Homeostatic model assessment for insulin resistance

HRP: Horseradish peroxidase

Hs-CRP: High sensitivity C reactive protein

ICC: Intraclass correlation coefficient

IR: Insulin Resistance

LAD: Left anterior descending

LCX: Left circumflex artery

LDL: Low density lipoprotein

LV: left ventricle

MAb: Monoclonal antibody

MCP: Monocyte chemotactic protein

MESA: Multi-Ethnic Study of Atherosclerosis

MDCT: Multidetector computed tomography

MI: Myocardial infacrtion

MRI: Magnetic resonance imaging

NAFLD: Non alcoholic fatty liver disease

PAT: Pericardial adipose tissue

PET: Positron emission tomography

RCA: Right coronary artery

RV: right ventricle

SI: Signal intensity

SIP: Signal intensity on In phase image

SOP: Signal intensity on Out of phase image

TFE: Turbo flash echo

TNF-α: Tumor necrosis factor-α

UCP1: uncoupling protein 1

VAT: Visceral adipose tissue

VLDL: Very low density lipoprotein

WHR: Waist hip ratio

Introduction

Introduction

1.1. Epicardial Adipose Tissue: Anatomic, Biochemical & Functional Characteristics

Our perception of adipose tissue (AT) has changed considerably over the last decades with the dramatic increase in the incidence of obesity and obesity-related comorbidities. AT is a loose association of lipid-filled cells called adipocytes, which are held in a framework of collagen fibers (Figure 1). 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.

AT is increasingly recognized as a vital complex endocrine organ which generates various bio-active molecules with profound local and systemic effects [1,2]. 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 comorbidities associated with excess body fatness[3–5], obesity has remained a puzzling condition for clinicians because of its remarkable heterogeneity[6]. 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 antiatherogenic effect [7], whereas accumulation of visceral AT (VAT) associates with increased prevalence of insulin resistance (IR), metabolic syndrome, and related CV complications [8].

Epicardial adipose tissue (EAT) is a particular form of VAT deposited around the heart and found in considerable quantities around subepicardial coronary arteries. There is a growing evidence suggests 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) [9–12].

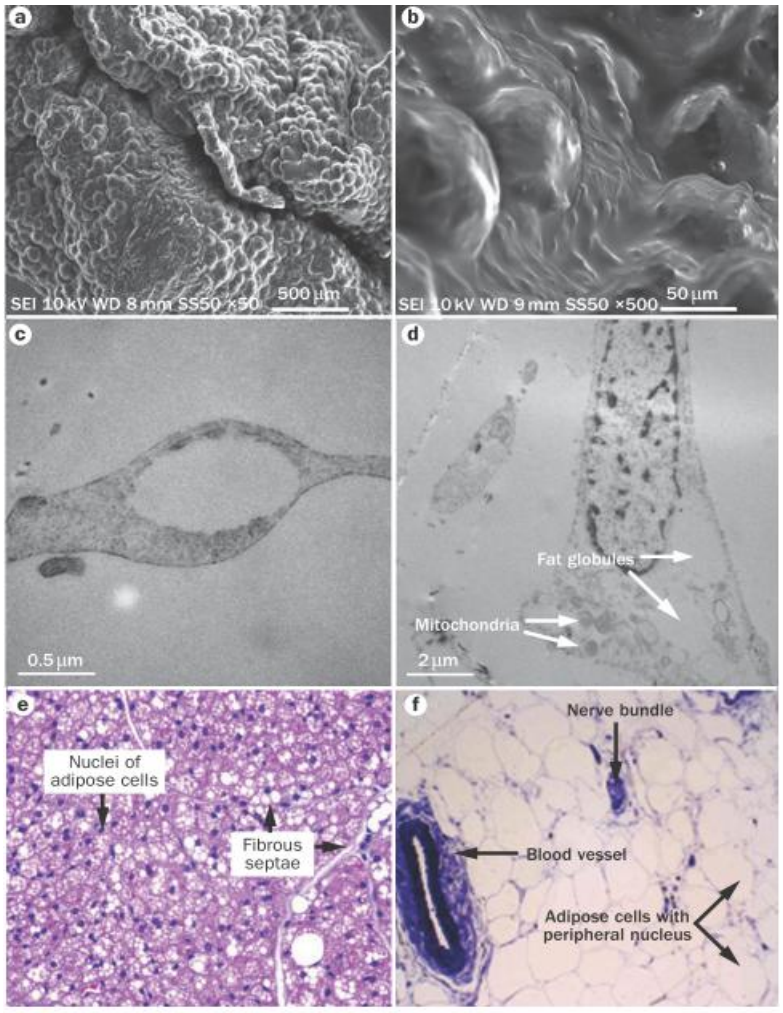

Figure 1: Ultrastructure of AT. Images of AT from outside the aortic valve and aorta at **(a**) low (×50) and **(b)** high (×500) magnifications obtained by scanning electron microscopy. The images show the 3D morphology of the adipose cells, which are rounded and bulging with adipose in an extracellular matrix. **(c,d)** The internal structure of adipocytes obtained by transmission electron microscopy. Each image shows an adipocyte full of fat globules. Lipid droplets in adipocytes: 1 µm-thick resin sections stained with toluidine blue show **(e)** multilocular adipocytes of brown AT, and **(f)** unilocular adipocytes of white adipose tissue with a characteristic signet-ring appearance (adapted from reference[6])

Anatomic Characteristics of Epicardial Adipose Tissue

The concept of cardiac adiposity, as a new CV risk factor and marker is rapidly emerging[13,14]. 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[9,15]. It is located between the myocardium and visceral pericardium around both ventricles of the heart, with variable extent and distribution patterns[9,14] (Figure 2). EAT is commonly found in the atrioventricular and interventricular grooves and along the major epicardial coronary arteries [9]. Minor foci of fat