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Ectopic Cardiac Depots, Inflammation and Cardiovascular Disease

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Abstract

Ectopic fat may cause anatomic and functional abnormalities in adipocyte and adipose tissue, resulting in imbalances in the endocrine and immune system. Adiposopathy may contribute to cardiovascular disease (CVD) through pericardiac and perivascular effects on the myocardium and blood vessels. Adiposopathy may also indirectly contribute to CVD promoting or worsening major CVD risk factors such as type 2 diabetes mellitus, hypertension and dyslipidemia. CVD is the most common cause of mortality among overweight individuals, but the pathophysiologic relationship between adiposity and CVD still is poorly understood, as evidenced by "obesity paradoxes". Underlying this uncertainty are suggestions that excessive body fat does not always increase the risk of CVD and, in some cases, may actually decrease such risks. This review aims to address the recent aspects of the relationships between ectopic fat, inflammation and CVD.

Keywords: Ectopic cardiac fat; Inflammation; Cardiac function; Atherosclerosis

Introduction

Obesity is associated with significant cardiovascular morbidity and mortality [1-3]. Epicardial fat is an active organ and source of several bioactive molecules that can affect cardiac morphology and function [4-11]. Because of the close anatomical relationship to the heart, and the absence of fascia boundaries, epicardial adipose tissue may locally interact and modulate the coronary arteries and myocardium through paracrine and direct secretion of anti-inflammatory and pro-inflammatory adipokines [12,13]. Epicardial fat tissue surrounding the heart, called epicardial or pericardial fat, encases the coronary arteries, and is therefore a subtype of the perivascular adipose tissue that surrounds blood vessels and is clinically related to atherosclerosis and major anthropometric and metabolic predictors of increased cardiovascular risk [14-20]. A relationship between epicardial fat thickness, inflammation and cardiovascular disease has been reported [7,20] although this relationship is still under question [21]. This review will explore the current understanding of ectopic cardiac adipose tissue storage, and existing research supporting an association between ectopic cardiac fat, inflammation and cardiovascular disease.

Ectopic Cardiac Fat Depots and Local Effects

Ectopic fat depots include accumulation of adipose tissue surrounding the heart and coronary arteries, or via lipid accumulation within cardiomyocytes. Adipose tissue surrounding the heart, called epicardial or pericardial fat, encases the coronary arteries, and is therefore a subtype of the perivascular adipose tissue that surrounds blood vessels.

Previous translational work has shown that perivascular adipose tissue possesses anti contractile properties, and secreted substances such as adiponectin and the adipocyte derived relaxing factor play a role in the vasoactive properties of perivascular fat [22,23]. Interestingly, the anti contractile property of perivascular adipose tissue is abolished with the development of obesity [22]. Furthermore, obesity appears to reduce the physiological effect of perivascular fat on smooth muscle cell migration in animal models [24]. These alterations in the function of perivascular fat appear to correlate with the infiltration of the adipose tissue by macrophages and upregulation of inflammatory adipokines [25].

Consistent with this finding, epicardial fat harvested at the time of coronary artery bypass surgery was found to have higher levels of proinflammatory mediators in comparison with subcutaneous fat [26]. Inflammation in the heart may be a contributor to insulin resistance. Cytokines impair insulin signaling by activating intracellular signaling kinases such as Jun N-terminal kinase that impairs insulin signaling by increasing the serine phosphorylation of insulin resistence substrate proteins [27]. It is possible that this mechanism may potentially occur in cardiomyocytes. It has been reported that high-fat feeding increased inflammation in the obese mouse heart, as evidenced by interleukin-6-mediated increases in macrophage and cytokine infiltration into the heart. In addition, glucose oxidation was reduced as a result of cardiac inflammation in an interleukin-6-dependent manner [28]. It remains to be demonstrated whether the local increase in myocardial inflammation directly contributes to impaired myocardial insulin action or the metabolic changes are secondary to systemic changes.

Population level research has supported the idea of a local toxic effect of pericardial fat. In the Framingham heart study, the volume of pericardial fat was associated with coronary artery calcium, but not cardio metabolic risk factors after Visceral Adipose Tissue (VAT) adjustment29. By contrast, VAT, which can be up to 20 times the volume of pericardial fat, was not associated with coronary artery calcium [29]. Similarly, pericardial fat was found to be associated with incident coronary heart disease in the multi-ethnic study of atherosclerosis (MESA) [30]. Additional research examining the associations of pericardial fat with measures of cardiac structure and function, and clinical cardiovascular disease, have shed further light on the idea of a local effect of pericardial fat [31,32]. First, pericardial fat volume assessed by computed tomography (CT) was found to be positively associated with (MRI) measured left atrial size in men [31]. Subsequent work supported these findings by demonstrating a positive association between pericardial adipose tissue and prevalent atrial fibrillation, which is known to be associated with left atrial size [33]. Although

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