Ectopic Fat Assessment Focusing on Cardiometabolic and Renal Risk

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It is well known that people with high levels of body fat are at higher risk for developing diabetes mellitus, kidney disease, and cardiovascular disorders. Since individuals who are slightly overweight, or even individuals of normal weight, can vary in body fat distribution, their metabolic profiles and the degree of association of these profiles with cardiometabolic risk factors may differ. Fat distribution might be more of a predictive factor for cardiorenometabolic risk than obesity itself, which has led researchers to investigate whether ectopic fat accumulation may partially account for the development of cardiorenometabolic disorders. In addition to visceral obesity, fat can accumulate in the liver and muscle, and these intrahepatic and intramuscular lipid stores are associated with insulin resistance and adverse metabolic phenotypes. More recently, pericardial fat, perivascular fat, and perirenal fat were found to be associated with coronary atherosclerosis, cardiovascular diseases, and kidney damage, respectively. Thus, regional fat distribution may play a key role in understanding the development of cardiorenometabolic diseases in nonobese people.

Keywords: Ectopic fat; Cardiorenometabolic risk; Imaging techniques

INTRODUCTION

Obesity and its complications have been increasing worldwide and are becoming big burdensome to both healthcare costs and mortality. Obesity, particularly when accompanied by an excess of visceral or ectopic fat, is a major risk factor for diseases, including insulin resistance, type 2 diabetes, nonalcoholic fatty liver disease, and cardiovascular disease [1]. In addition to overall obesity, ectopic fat and fat accumulation in specific compartments of the body have been found to detrimentally contribute to various health conditions. Ectopic fat is defined as fat depots in various organs or tissues, including fat in the liver and muscle, pericardial and perivascular fat, and fat around the kidney. Fat depots in the liver or muscle tissue can increase adverse cardiometabolic risk by affecting systemic energy metabolism. Pericardial fat, perivascular fat, and renal sinus fat may exert their primary effects on adjacent anatomic organs by direct lipotoxicity, and they act indirectly by cytokine secretion. Additionally, pericardial fat is known to be associated with coronary atherosclerosis. Perivascular fat may play an independent role in adverse vascular biology, contrib-

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uting to arterial stiffness. Renal sinus fat is a unique fat depot that may confer additional cardiometabolic risk such as high blood pressure. Thus, exploring ectopic fat depots may contribute to understanding the link between body composition and cardiometabolic risk.

In this article, we investigated the clinical implications of ectopic fat depots from a cardiorenometabolic perspective, and we assessed the imaging techniques used to measure the fat depots.

FAT ACCUMULATION IN THE LIVER

Fatty liver contributes to cardiometabolic risk in several ways [2]. For example, fat deposition in the liver induces hepatic insulin resistance and also stimulates the production of inflammatory cytokines [3]. Additionally, fat depots in the liver induce hepatic very low density lipoprotein production through apolipoprotein B metabolism and *de novo* lipogenesis [4]. These findings support a significant association between fat accumulation in the liver and systemic inflammation and atherogenesis.

Classically, ultrasonography has been used to define fatty liver, but it is limited by its lack of discrete quantification [5]. Conversely, computed tomography (CT) is used to evaluate fat accumulation in the liver qualitatively and quantitatively, but CT carries the risk of radiation exposure [6]. Recently, a noninvasive method, volume-localized ^{1}H-magnetic resonance spectroscopy (MRS), was established [7], which offers the unique ability to measure intrahepatic lipid content *in vivo*. However, this approach is limited by cost due to the required specialized machinery.

FAT ACCUMULATION IN MUSCLE

Skeletal muscle tissue is the main destination for insulin-stimulated glucose disposal and is considered to be a principal determinant of systemic insulin resistance [8]. One potential mechanism to explain the relationship between intramuscular lipid and insulin resistance is the apparent defects in fatty acid metabolism in people with high intramuscular fat [9]. Specifically, defects in the fatty acid oxidation pathway lead to diminished use of fatty acids and increased esterification and lipid storage within skeletal muscle. These impairments in fatty acid metabolism result in metabolic abnormalities. Thus, derangements in fatty acid and triglyceride metabolism during fat accumulation in skeletal muscle contribute to cardiovascular risk.

As noninvasive methods, dual-energy X-ray absorptiometry (DXA) and CT have been used to measure fat deposition in muscle [10,11]. The advantage that DXA offers is its ability to measure upper and lower extremity fat amount separately with a single scan image. CT technique can indirectly estimate the degree of fat content in the muscle by measuring the Hounsfield unit range [12]. Recently, another noninvasive method, volume-localized ^{1}H-MRS, was established, and this method offers exquisite discrimination of fat deposition, with the ability to differentiate between intramyocellular and extramyocellular fat deposits in muscle tissue [7].

PERICARDIAL FAT

Fat depots around the heart and coronary arteries can be classified into the following three categories: 1) pericardial fat, which is the fat located between the internal border of the mediastinum and the external surface of the parietal pericardium; 2) epicardial fat or fat tissue within the pericardial sac, mainly in the atrioventricular and interventricular grooves; and 3) pericoronary fat surrounding the coronary arteries within the visceral epicardium. Pericardial fat may have direct effects on the pathogenesis of coronary atherosclerosis through a paracrine role [13]. Specifically, the adipocytokines released from pericardial fat may increase vessel wall inflammation and may stimulate the progression of atherosclerosis via outside-to-inside signaling [14].

By using transthoracic echocardiography, epicardial fat thickness can be measured on the free wall of the right ventricle from parasternal views [15]. Compared to echocardiography, multidetector CT is volumetric, and three-dimensional reconstruction is possible [16]. Also, CT has an advantage in its reproducibility of the quantification of pericardial fat volume. In addition to these methods, the amount of epicardial fat can also be measured in consecutive short-axis views by magnetic resonance imaging (MRI) using the three-dimensional summation of slices method [17].

PERIVASCULAR FAT

Vasocrine signaling from perivascular fat was proposed to have a vasoregulatory role in local deposits of fat around the arterioles supplying skeletal muscle [14]. Perivascular fat may possibly contribute to insulin resistance through direct vascular effects leading to reduced capillary cross-sectional area in the muscle, which, in turn, affects muscular blood flow and

glucose uptake. Since perivascular adipose tissue expresses cytokines that stimulate inflammation and inhibit insulin signaling pathways, perivascular fat induces impairment of endothelium-dependent vasodilatation and leads to vascular complications [14,18]. Thus, perivascular fat might contribute to the development and progression of atherosclerosis.

Perivascular adipose tissue can be measured by multidetector CT and MRI. In a study using multidetector CT, abdominal periaortic adipose tissue was defined by a 5-mm cylindrical region of interest around the aortic wall [19]. Additionally, high-resolution MRI can quantify perivascular fat around arteries [20].

RENAL SINUS FAT

Fat accumulation in and around the kidney may also play a distinct role in renal function and blood pressure [21]. In an obese animal model, increased renal sinus fat was associated with increases in blood pressure and renal interstitial pressure through the compression of vessels exiting the kidney [22]. In another animal mode, lipid accumulation within the renal parenchyma induced lipotoxicity, inflammation, oxidative stress, and renal fibrosis [23]. These studies support the association of renal lipid accumulation with concomitant structural and functional changes in the kidney and vasculature.

Renal sinus fat accumulation can be measured from a single-slice area measurement of the kidney by using multidetector CT [24]. Pararenal and perirenal fat thickness can be measured from the inner side of the abdominal musculature to the surface of the kidney by ultrasonography [25].

CONCLUSIONS

The present article summarized the evidence regarding the metabolic correlates of ectopic fat depots. Potential mechanisms for the association between body fat distribution and cardiorenometabolic disorders were reviewed. Collectively, current evidence has led to the hypothesis that ectopic fat may partially contribute to cardiorenometabolic disorders. Further investigation to identify additional benefit of targeting fat depots at specific locations in individuals with the greater risk is intriguing. Also, prospective studies focusing on ectopic fat accumulation with cardiorenometabolic events are warranted.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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