Links Between Ectopic Fat and Vascular Disease in Humans

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Abstract—The average of overweight individual can have differential fat depots in target organs or specific compartments of the body. This ectopic fat distribution may be more of a predictive factor for cardiovascular risk than obesity. Abdominal visceral obesity, a representative ectopic fat, is robustly associated with insulin resistance and cardiovascular risk. Fat depots in the liver and muscle tissue cause adverse cardiometabolic risk by affecting glucose and lipid metabolism. Pericardial fat and perivascular fat affect coronary atherosclerosis, cardiac function, and hemodynamics. Fat around the neck is associated with systemic vascular resistance. Fat around the kidney may increase blood pressure and induce albuminuria. Fat accumulation in or around the pancreas alters glucose metabolism, conferring cardiovascular risk. Ectopic fat may act as an active endocrine and paracrine organ that releases various bioactive mediators that influence insulin resistance, glucose and lipid metabolism, coagulation, and inflammation, which all contribute to cardiovascular risk. Because both obese and apparently lean individuals can have ectopic fat, regional fat distribution may play an important role in the development of cardiovascular diseases in both nonobese and obese people. (Arterioscler Thromb Vasc Biol. 2014;34:1820-1826.)

Key Words: body fat distribution ■ cardiovascular diseases ■ fatty liver ■ insulin resistance ■ intra-abdominal fat

Obesity and its complications have been increasing worldwide and are becoming a huge burden to both human health and healthcare costs.1-3 In addition to overall obesity, ectopic fat has been found to contribute to cardiovascular disease (CVD). Ectopic fat is fat accumulation in or around specific organs or compartments of the body as the omentum, liver, muscle, and pancreas. Fat may accumulate around the heart, blood vessels, kidney, and neck. Fat depots in the liver or muscle tissue can increase cardiovascular risk by affecting lipid and glucose metabolism, particularly when accompanied by inflammation. Pericardial fat, perivascular fat, pericoronary fat, and myocardial fat may exert their harmful effects on the heart and blood vessels by direct lipotoxicity and indirect cytokine secretion. Renal sinus fat is a unique fat depot that may confer additional cardiovascular risk such as microalbuminuria and high blood pressure. Recently, researchers highlighted the concept of fat accumulation in the pancreas (fatty pancreas) associated with altered glucose metabolism and insulin resistance, which may also contribute to cardiovascular risk. Collectively, the unique concept of ectopic fat storage in key target organs contributes to the understanding of a pathogenic role of ectopic fat in cardiovascular risk (Figure 1).

This review summarizes the clinical implications of ectopic fat depots from a cardiovascular perspective. We focused on the underlying mechanisms between ectopic fat depots and CVD derived mostly from human studies. Subcutaneous adipose tissue was excluded from this review because of the uncertainty of its relation with vascular diseases in humans.

Fat in the Abdomen

Increased abdominal visceral adipose tissue (VAT) is associated with a clustering of metabolic risk factors as well as insulin resistance.4-7 Several cross-sectional studies have shown that patients with subclinical atherosclerosis or overt coronary artery disease have greater VAT than those without, even after adjusting for body mass index (BMI).5,8-10 In stark contrast, relatively small numbers of studies reported an independent role of VAT in cardiovascular events.11,12 A 10-year follow-up study with Japanese Americans showed that VAT was an independent risk factor for incident coronary artery disease.11 Similarly, a study with participants from the Framingham Heart Study found that visceral adiposity was associated with incident CVD after adjustments for clinical risk factors and overall adiposity.12 Abdominal VAT accumulation was positively associated with the progression of coronary noncalcified plaque.13 Several mechanisms have been suggested to explain the association of VAT with cardiovascular risk.14,15 One such mechanism is that VAT has increased lipolytic activity and, therefore, increases delivery of free fatty acids to the liver, ultimately leading to insulin resistance.16 Low-grade inflammation often presents in increased VAT. This inflamed fat can affect immunity.17 Inflamed fat depots produce atherosclerosis-prone cytokines, the circulating concentrations of which...
are modulated by metabolic or inflammatory processes.\textsuperscript{18,19} Indeed, in the Framingham Heart Study, VAT was positively related to inflammation and oxidative stress.\textsuperscript{20}

Obesity in humans is associated with increases in oxidative stress markers such as isoprostanes and protein-bound carbonyls in adipose tissue.\textsuperscript{21,22} The increased reactive oxygen species in large VAT is accompanied by an increase in mRNA expression levels of NADPH oxidase subunits, an enzyme complex that generates reactive oxygen species, and a decrease in mRNA expression levels and activities of antioxidant enzymes such as glutathione peroxidase and Cu/Zn superoxide dismutase.\textsuperscript{23} Several animal studies suggest other mechanisms. Activity of methionine sulfoxide reductase A, an antioxidant defense enzyme, was reduced by $\approx 25\%$ in the visceral adipose of Zucker diabetic fatty rats.\textsuperscript{24} S-glutathionylation was decreased in the adipose tissue of obese rats.\textsuperscript{25} These data provide that VAT alters the redox system, resulting in an increase of reactive oxygen species production, which might be involved in the pathogenesis of insulin resistance in obesity.

Hypermorphed adipose tissue is characterized by an infiltration of macrophages and is a major source of proinflammatory cytokines including interleukin-6 and tumor necrosis factor-$\alpha$.\textsuperscript{26} In obese patients with high VAT accumulation, the systemic renin–angiotensin system (RAS) is impaired.\textsuperscript{27} There are several possible physiological and molecular mechanisms that link VAT with the RAS: increased secretion of angiotensinogen from adipocytes, interaction between hyperinsulinemia induced by increased VAT and activation of angiotensin type 1 receptors, and influence of adipocytokines (tumor necrosis factor-$\alpha$ and interleukin-6) released from VAT on RAS system.\textsuperscript{24,28} The increased activity of the RAS in subjects with high VAT volume may play a key role in hypertension and its cardiovascular complications. For instance, VAT volume was significantly associated with the prevalence of microalbuminuria in low-risk, nondiabetic subjects.\textsuperscript{29} VAT is also associated with increased levels of plasminogen activator inhibitor-1, reflecting depressed fibrinolysis with a greater tendency toward clinically relevant thrombosis.\textsuperscript{30} Bioactive mediators released from VAT combined with inflammation, oxidative stress, and activated RAS all lead to endothelial dysfunction and atherosclerosis.\textsuperscript{31,32,33} The elderly patients compared with young patients with the same BMI had increased VAT, which linked to atherosclerotic biomarkers and subclinical atherosclerosis.\textsuperscript{34}

Computed tomography (CT), MRI, and new dual-energy x-ray absorptiometry techniques have been used to measure abdominal fat differentially from subcutaneous adipose tissue.\textsuperscript{3,35,36} Ultrasonography is also a method used to estimate abdominal VAT.\textsuperscript{37}

### Nonalcoholic Fatty Liver Disease

There is substantial evidence supporting a relation between nonalcoholic fatty liver disease and CVD. In the Framingham Heart Study, fatty liver was associated with a clustering of cardiovascular risk after adjustment for other fat depots including VAT.\textsuperscript{38} Another study reported that intrahepatic lipid deposits were more closely linked with cardiovascular complications than with VAT.\textsuperscript{39} More directly, nonalcoholic fatty liver disease has been found to be an independent predictor of incident cardiovascular events in patients with type 2 diabetes mellitus as well as normal subjects.\textsuperscript{40–42}

Several mechanisms have been proposed for the association of fatty liver with cardiovascular risk.\textsuperscript{38} The liver plays a central role in lipid metabolism and storage. In addition to the critical role in triglyceride synthesis and storage, hepatocytes contain lipid droplets in the lumen of the endoplasmic reticulum where very low-density lipoprotein is assembled.\textsuperscript{43} Thus, the liver secretes triglycerides into the blood in apolipoprotein B–containing very low-density lipoprotein particles. Fatty liver leads to hepatic insulin resistance, which induces hepatic very low-density lipoprotein production via changes in the rate of apolipoprotein B synthesis and degradation or de novo lipogenesis.\textsuperscript{44}

Furthermore, fatty liver stimulates the production of inflammatory cytokines.\textsuperscript{45} In particular, nonalcoholic steatohepatitis may instigate the pathogenesis of CVD through the systemic release of several inflammatory, hemostatic, and oxidative stress mediators.\textsuperscript{46} Fatty liver may also play a part in cardiac dysfunction. Hepatic triglyceride content in type 2 diabetes mellitus was associated with decreased myocardial perfusion.\textsuperscript{47} Another study also showed that high triglyceride content in the liver was associated with myocardial dysfunction in type 2 diabetes mellitus.\textsuperscript{48} These results support that fat accumulation in the liver may play an important role in the atherosclerotic milieu by promoting insulin resistance and systemic inflammation.

Many studies have tried to measure fat accumulation in the liver noninvasively. Classically, ultrasonography has been

![Figure 1. Ectopic fat storage in key target organs or compartments contributing to atherosclerosis and cardiovascular risk.](image-url)
used to define fatty liver, but it has the limitation of quantification. Recently, CT has been used to measure fat accumulation in the liver, but CT has the risk associated with radiation exposure. The noninvasive volume-localized 1H magnetic resonance spectroscopy (MRS) has been used experimentally. This method has the unique advantage of measuring intrahepatic lipid content accurately. However, because of the high cost of the specialized machinery, it is not widely used.

**Intramuscular Fat**

In patients with diabetes mellitus, muscle density assessed by quantitative CT (representation of higher fat infiltration) was observed to be lower than that in patients without diabetes mellitus, even after adjusting for BMI. Individuals with insulin resistance had greater intramuscular fat deposits than those with insulin sensitivity, showing that fat deposits in muscle tissue contribute to impaired glucose uptake. Several studies with MRS have demonstrated that the accumulation of intramyocellular triglycerides induces the development of insulin resistance in various populations. Furthermore, patients with diabetes mellitus who had more fat in muscle tissue had greater carotid intima-media thickness than their healthy counterparts. These results provide evidence that intramuscular fat depot is associated with atherosclerosis via increasing insulin resistance independent of overall obesity.

Skeletal muscle tissue is the main destination for insulin-stimulated glucose disposal and fatty acid metabolism, which are principal determinants of systemic insulin resistance. The defects in fatty acid metabolism in people who have excessive intramuscular fat support that fat accumulation in the muscle is closely associated with insulin resistance. A defect in mitochondrial oxidative phosphorylation and fat accumulation in muscle was found to be related to insulin resistance in humans. Thus, mitochondrial dysfunction in the muscle with impairments in fatty acid and triglyceride metabolism is a key in the cause of insulin resistance, leading to cardiometabolic abnormalities.

There are several methods to measure fat accumulation in the muscle tissue. CT has been used to measure fat deposition in muscle. However, CT scan is an indirect method that estimates the fat content by measuring the Hounsfield unit. Dual-energy x-ray absorptiometry is also frequently used. The advantage that dual-energy x-ray absorptiometry offers is its ability to measure upper and lower extremity fat amounts separately with a single scan image.

Volume-localized 1H-MRS can also be used in fat measurement in the muscle. This method has the unique advantage differentiating between intramyocellular and extramyocellular fat deposits.

**Fat in the Neck**

Fat in the neck, a proxy for upper body fat, is a unique ectopic fat depot that contributes to additional cardiovascular risk. Several studies have shown that fat in the neck is positively correlated with visceral fat, insulin resistance, and metabolic syndrome. Increased fat deposition around the neck is associated with sleep apnea syndrome, which increases cardiovascular risk through hemodynamic and hematologic changes. Altered endothelial permeability and diminished peripheral blood flow that accompanies a larger neck circumference may promote insulin resistance in metabolically active tissues. In addition, repeated hypoxia and reoxygenation during sleep by airway obstruction provoked by a large fat accumulation around the neck may increase the production of reactive oxygen species, which also play an important role in the development of CVD. However, whether and how fat in the neck is associated with cardiometabolic risk factors independently of VAT should be further elucidated in mechanistic studies.

CT and MRI techniques can measure fat accumulation in the neck with the advantage of distinguishing deep fat from subcutaneous fat.

**Fat Depots Around the Heart and Coronary Arteries or in the Myocardium**

Fat around the heart has been reported to be associated with coronary calcification, atheromatous plaques, and coronary artery disease with or without VAT. Fat located around the heart is divided into 2 types: pericardial fat, which is located between the external surface of the parietal pericardium and the internal border of the mediastinum, and epicardial fat, which is located within the pericardial sac, mainly in the atrioventricular and interventricular grooves and around the atria and ventricles.

In the Framingham Heart Study, the amount of pericardial fat was positively associated with coronary artery calcification independent of conventional risk factors. Furthermore, individuals with more pericardial fat had reduced left ventricular function or increased risk of atrial fibrillation. These findings suggest the potential locally toxic effect of pericardial fat on cardiac function and conduction. Thus, pericardial fat has a pathogenic effect on either the structural or functional aspects of cardiovascular risk.

Fat depots around the heart and coronary arteries can be classified into pericardial fat, epicardial fat, and pericoronary fat. Pericardial fat has direct effects on the development of coronary atherosclerosis in a paracrine manner.

In addition, epicardial fat releases many cytokines such as leptin, resistin, tumor necrosis factor-α, interleukin-6, visfatin, and chemerin. Leptin was found to exacerbate endothelial dysfunction via a protein kinase Cβ-dependent pathway. It has been recently reported that pericoronary adipocytes have the potential to modulate the inflammatory process between endothelial and inflammatory cells. An animal study has shown that perivascular fat may act differently according to anatomic location. These data suggest that factors released from coronary adipose tissue and the location of fat around vessels may affect vascular functions differentially in insulin-resistant milieu.

Fat depots around the heart and coronary arteries seem to stimulate the progression of atherosclerosis via outside-to-inside signaling. Fat around the heart is known to be associated with oxidative stress, activation of the coagulation cascade, disturbances in the RAS, and enhanced lipid oxidation, which generates oxidized low-density lipoprotein. Excessive fat can also accumulate in the myocardium. The ectopic fat depot inside the heart may induce cardiomyopathy and subsequently heart failure. Histological evaluation of patients with heart failure and severe metabolic dysregulation revealed an overload of intramyocardial triglycerides. Accumulation of large amounts of lipid in the myocardium...
may induce apoptosis of cardiomyocytes and cardiac dysfunction. More specifically, increased levels of fatty acid transfer proteins in the myocardium may lead to cardiomyopathy.87

Epicardial fat thickness can be measured on the free wall of the right ventricle using echocardiography.88 A recently developed multidetector-row CT technique offers volumetric assessment of fat depots around the heart with high reproducibility.74 MRI using a 3-dimensional approach can also measure the amount of fat around the heart.89 Lipid content in cardiac muscle can be quantified using 1H-MRS.90

**Fat Around Kidney**

Fat accumulation in and around the kidney seems to play an important role in maintaining blood pressure and kidney function.91,92 In a study with middle-aged subjects at risk for cardiovascular events, renal sinus fat was associated with high blood pressure after accounting for conventional risk factors for hypertension and abdominal fat depots.92 A recent study with individuals at diabetic risk reported that fat depots in the renal sinus area was independently associated with microalbuminuria, which is a robust risk factor for future CVDs.92 Estimated glomerular filtration rate and uricemia were associated with para- and perirenal fat, even after adjusting for BMI in patients with type 2 diabetes mellitus.93 In the Framingham Heart Study, renal sinus fat area was associated with hypertension after accounting for VAT.94 These data suggest that fat accumulation in the renal sinus may contribute to the development of CVD via vascular tone and albuminuria.

We can deduce the underlying mechanisms connecting renal sinus fat and CVD from animal studies showing that the elevation of compressive forces by fat depots in the renal sinus constricted low-pressure conduits such as renal veins and ureters.95,96 Fat accumulation in the kidneys was associated with glomerulosclerosis and proteinuria with increased expression of sterol regulatory element–binding protein.97 Thus, renal sinus fat or fatty kidney may induce structural and functional damage in the kidney and subsequently increase systemic vascular resistance and cardiovascular risk.

By using ultrasonography, fat thickness in the pararenal and perirenal area can be measured from the inner side of the abdominal musculature to the surface of the kidney.93 Fat accumulation around kidney can also be measured from a single slice of the kidney by using multidetector-row CT.98

**Fatty Pancreas or Fat Accumulation in and Around the Pancreas**

Fat can accumulate in and around the pancreas. Several studies showed that intrapancreatic fat amount was associated with pancreatic β-cell dysfunction.99–101 Old age, high BMI, low physical activity, and dyslipidemia may induce fat accumulation in the pancreas,99,102 with ensuing pancreatic dysfunction.

Although there have been limited data linking fat depots in the pancreas with cardiovascular risk directly, pancreatic fat accumulation may contribute to cardiovascular risk by inducing insulin resistance and aggravating glucose metabolism.

The measurement of pancreatic fat accumulation in humans is challenging because the pancreas is located in the retroperitoneum. Variable shape and vague boundaries make the pancreas difficult to measure. Compared with fatty liver, the assessment of pancreatic fat by imaging techniques has not received much attention. Previously, a few empirical studies measured fat accumulation in the pancreas using CT and MRI techniques.99,103 Concerns with these studies include using a machine with low resolution, small number of study subjects, and the lack of detail in measurement methodologies. A recent study reported that CT attenuation indexes can be used to quantify pancreatic fat, which was validated by histological assessment of pancreatic fat fraction.104 Our group also showed that pancreatic fat was quantitatively measured by multidetector-low CT with Hounsfield unit range, which was associated with impaired glucose metabolism.105 In another recent study with 685 healthy volunteers, the subjects who

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Figure 2. Mechanisms of various ectopic fats related with atherosclerosis and cardiovascular diseases. FFA indicates free fatty acid; RAS, renin-angiotensin system; ROS, reactive oxygen species; TG, triglyceride; and VLDL, very low-density lipoprotein.
had both fatty pancreas measured by fat water MRI and fatty liver by MRS had a higher insulin resistance index than those who had either condition alone.106

Summary and Conclusions

This article summarized various types of ectopic fat and their potential mechanisms for their associated cardiovascular risk (Figure 2). Although the mechanisms of ectopic fat depots have not been well studied, a growing body of evidence supports an independent contribution of ectopic fat deposition to cardiovascular risk beyond those implicated in general obesity. Based on many studies, ectopic fat seems to act as an active endocrine and paracrine organ, secreting several cytokines that influence insulin resistance and diverse processes of atherosclerosis.107 The impact of ectopic fat on CVD progression may be limited in the initial stages but its long-term effects can be substantial because it has both local effects on key target organs and systemic effects on the cardiovascular system. Longitudinal studies investigating independent roles of ectopic fat depot on future cardiovascular events are warranted. Interventional studies to prove the additional benefits of targeting fat depots in specific organs or areas in individuals with cardiovascular risk may also be required for definitive proof.

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