Ectopic Fat Depots and Cardiovascular Disease

Kathryn A. Britton, MD; Caroline S. Fox, MD, MPH

Obesity is increasingly recognized as a heterogeneous condition with variable cardiovascular risk in the setting of similar levels of body mass index. Ectopic fat depots may contribute to obesity-mediated vascular disease and explain part of this risk differential. This review will explore the current understanding of the biology of ectopic adipose tissue storage, its quantification and classification, and existing research supporting an association between ectopic fat and cardiovascular disease.

Obesity is associated with significant cardiovascular morbidity and mortality, and is recognized as a major public health concern. Although useful clinically and in epidemiologic studies, the classification of obesity using body mass index (BMI) does not fully encompass the complex biology of excess adiposity. Excess body fat is now recognized as a heterogeneous condition in which individuals with similar levels of BMI may have distinct metabolic and cardiovascular disease risk. Variation in body fat distribution provides 1 potential explanation for some of the risk differential that persists after accounting for BMI and standard risk factors. The study of ectopic adipose tissue depots, which surround organs and blood vessels, focuses on the quantification of these different fat depots and their potential systemic and local consequences.

Waist circumference was one of the earliest means of quantifying body fat distribution, and some clinical guidelines have recommended measurement of waist circumference to provide additional information regarding cardiovascular risk. However, waist circumference consists of both subcutaneous adipose (SAT) (classically nonectopic) and visceral adipose tissue (VAT) (classically ectopic). This is important because VAT is associated with more adverse levels of metabolic risk factors compared with SAT. In addition, seminal work in mice has shown that transplantation of SAT, but not VAT, to an intra-abdominal site resulted in beneficial effects on metabolism. Taken together, these findings suggest that information about body fat distribution beyond waist circumference may provide important insights into metabolic and cardiovascular disease risk.

Definition, Pathophysiology, and Quantification of Ectopic Fat Depots

Some amount of adipose tissue surrounds several organs and has been shown to serve a physiological role. Ectopic fat is defined by excess adipose tissue in locations not classically associated with adipose tissue storage. There are several potential mechanisms that might explain the tendency to deposit adipose tissue in ectopic versus nonectopic depots. One hypothesis suggests that, in states of positive energy balance, free fatty acids are initially stored subcutaneously, but once the capacity of SAT is reached, storage shifts to ectopic sites, including the viscera, heart, and vasculature. The most extreme manifestation of this results in lipodystrophy, characterized by a paucity of subcutaneous fat with resultant deposition ectopically. This failure of SAT to store additional free fatty acids is believed to result from a failure of proliferation and differentiation of adipocytes leading to subcutaneous adipose hypertrophy as opposed to hyperplasia. Consistent with this theory, the degree of subcutaneous abdominal adipose cell hypertrophy has been shown to predict the development of type 2 diabetes mellitus. In addition, thiazolidinediones, which improve insulin sensitivity, have been shown to promote differentiation of new fat cells in subcutaneous fat without an increase in visceral fat. Taken together, these data suggest that ectopic fat deposition may result from the failure of SAT to act as a metabolic sink.

The determinants of subcutaneous versus ectopic fat are likely multifactorial, and include age, sex, race, smoking, nutritional and other environmental factors, and genetic factors. One newly appreciated contributor is the angiogenic capability of SAT. Recent work has shown that, in general, SAT has a higher ability than VAT to expand its capillary network. Specifically, SAT explants developed more capillary branches in comparison with VAT explants, and demonstrated a higher rate of growth when observed in culture. In addition, SAT from insulin-sensitive individuals demonstrated higher expression of genes known to be associated with angiogenesis. However, this greater angiogenic capacity of SAT decreased as BMI increased from the overweight to obese range, and this decrease was associated with adverse metabolic features. This lower angiogenic capacity of SAT with increasing BMI may contribute to the lower adipose tissue blood flow demonstrated in SAT in the setting of obesity. This decreased blood flow was associated with hyperoxia, as opposed to hypoxia, and may reflect decreased oxygen consumption in SAT with the development of obesity.

The growing appreciation of the potential importance of ectopic fat deposits in cardiovascular risk has led to interest in more direct quantification of the different adipose tissue depots. Multidetector computed tomography (MDCT), MRI, ultrasonography, and 1H magnetic resonance spectroscopy have all been used to quantify adipose tissue amount or lipid content within an organ (Table). There are advantages and disadvantages with each of these techniques. The ability to
quantify adipose tissue depots noninvasively has led to an increase in population-based analyses examining the association of various fat depots with both systemic and local manifestations of disease.5,16–18 These studies have taken the knowledge of fat depot-specific biology gleaned from basic and translational science and examined associations on a population level.

Classification and Subtypes of Ectopic Fat
Ectopic fat depots can be subdivided based on their location and their association with either potential systemic or local effects (Figure). Ectopic fat depots with predominantly systemic effects include VAT, intrahepatic fat (also known as fatty liver), and intramuscular fat. Ectopic fat depots with potential local effects include pericardial (or the related epicardial or pericoronary fat), renal sinus fat, myocardial steatosis, and perivascular fat.

Ectopic Fat Depots With Predominantly Systemic Effects
Although the association between obesity, body fat distribution, and metabolic derangements is now well established, the underlying mechanisms remain incompletely understood.13 Ectopic fat depots play an important role in several of the hypotheses postulated to explain the association of body fat distribution and cardiovascular disease.13 First, with the development of obesity, VAT becomes infiltrated with macrophages, and there is upregulation of a variety of adipokines.19 These adipokines have been shown to be important in the development of inflammation and insulin resistance.19 Alternatively, VAT may not be causally related to the development of metabolic disease, but it may serve as a marker of fat deposition in other ectopic locations. The accumulation of adipose tissue in organs integral to glucose and insulin metabolism (the liver and muscle) and lipid metabolism (the liver) are then directly postulated to contribute to the development of metabolic derangements.20,21 Although intrahepatic fat and intramuscular fat have a volume that is much smaller than VAT, they may have systemic effects that contribute to systemic metabolic disease.20,21 However, the relative importance of these various fat depots and their contributions to systemic metabolic derangements remain unclear, and is an active area of investigation.

Findings from population studies have provided additional insights into the associations of ectopic fat depots with

Table. Imaging Modalities for Assessment of Ectopic Fat

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Ectopic Fat Imaged</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound</td>
<td>Epicardial/Pericardial, Fatty Liver</td>
<td>Extremely safe, Relatively inexpensive, Often performed for other clinical indications</td>
<td>Pericardial fat is only measured over the right ventricle. This does not take into account variations in fat deposition over the heart surface, Obesity may limit image quality, Fatty liver assessment is less quantitative than other methods, Sensitivity and specificity of fatty liver lower than other methods</td>
</tr>
<tr>
<td>Multidetector Computed Tomography (MDCT)</td>
<td>Pericardial, Pericoronary, Thoracic Periaortic, Visceral, Fatty Liver, Renal Sinus</td>
<td>Easy to perform, Often performed for other indications, Allows volumetric assessment of adipose tissue, Submillimeter resolution, Excellent reproducibility</td>
<td>Radiation exposure, May not be able to accommodate individuals with severe obesity</td>
</tr>
<tr>
<td>Magnetic Resonance Imaging (MRI)</td>
<td>Pericardial, Visceral, Perivascular, Intra-hepatic, Renal sinus, Intra-muscular (skeletal)</td>
<td>Gold standard in assessment of visceral adipose tissue, No radiation or iodinated contrast required, Can assess multiple fat depots</td>
<td>More expensive than either MDCT or echocardiography, Exam more time consuming and less tolerated by patients, May not be able to accommodate individuals with severe obesity</td>
</tr>
<tr>
<td>1H Magnetic Resonance Spectroscopy</td>
<td>Intra-myocardial, Intra-hepatic, Intra-pancreatic, Intra-muscular (skeletal)</td>
<td>Can measure lipid content within an organ, Noninvasive, No radiation or iodinated contrast required, Most reliable imaging quantification method for these fat depots</td>
<td>Not currently used clinically, Uncommonly performed for other indications</td>
</tr>
</tbody>
</table>

Figure. Ectopic fat depots and their potential systemic and local effects.
predominantly systemic effects and cardiovascular disease. Although both SAT and VAT are associated with adverse metabolic risk factors, only VAT remains an important correlate of risk after accounting for indices of generalized adiposity. Another important finding is the sexual dimorphism present in body fat distribution and the consistent findings that VAT is more strongly associated with metabolic risk in women as compared to men. Inflammation and oxidative stress may additionally contribute to the association of both SAT and VAT with metabolic risk factors, and both of these fat depots were associated with measures of inflammation and oxidative stress. Although VAT was more strongly associated with urinary isoprostanes and monocyte chemoattractant protein-1, VAT and SAT demonstrated generally equivalent associations with circulating biomarkers of inflammation. Taken together, these findings suggest that circulating markers of inflammation are unlikely to explain the excess risk associated with VAT in comparison with SAT.

Population-level studies have also provided support for the potential importance of fatty liver in the development of insulin resistance and the metabolic syndrome. In adults, fatty liver assessed by MDCT was associated with markers of lipid and glucose metabolism, including insulin resistance, even after adjustment for VAT. Similarly, in overweight and obese children, metabolic syndrome was associated with the presence of biopsy-proven fatty liver even after matching for age, sex, and the degree of obesity, and adjustment for race, ethnicity, and hyperinsulinemia, as well. Although these findings are intriguing, their observational nature precludes inferences of causality. Additional research is necessary to further delineate the relationship between VAT and other ectopic fat depots with potential systemic effects and their role in the development of metabolic disease.

**Ectopic Fat Depots With Predominantly Local Effects**

In contrast to the ectopic fat depots with predominantly systemic metabolic effects, fat depots surrounding the heart and blood vessels and within the renal sinus are postulated to have primarily local effects. The theory of a local toxic effect of excess adipose tissue is supported by multiple lines of evidence from basic science, translational science, and epidemiology. This idea of a direct effect of adiposity on an organ was postulated in the early 20th century, and this theory has gained renewed interest with the increased availability and technological advances in imaging techniques.

Increasing body weight may directly influence the heart by at least 2 mechanisms. These 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 anticontractile properties, and secreted substances, including adiponectin and the adipocyte-derived relaxing factor, play a role in the vasoactive properties of perivascular fat. However, this anticontractile property of perivascular adipose tissue is abolished with the development of obesity. Furthermore, in animal models, obesity appears to reduce the physiological effect of perivascular fat on smooth muscle migration. These derangements in the function of perivascular fat appear to be related to infiltration of the adipose tissue by macrophages and upregulation of inflammatory adipokines. 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.

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 cardiometabolic risk factors (after VAT adjustment). By contrast, VAT, which can be up to 20 times the volume of pericardial fat, was not associated with coronary artery calcium. Similarly, pericardial fat was found to be associated with incident coronary heart disease in the Multi-Ethnic Study of Atherosclerosis. Additional work examining 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. First, pericardial fat volume assessed by MDCT was found to be positively associated with MRI-measured left atrial size in men. 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. By contrast, although pericardial fat was associated with left ventricular mass, this association did not persist after additional adjustment for VAT. These findings suggest that the systemic effects of obesity appear to outweigh any local effect of pericardial fat in the case of left ventricular mass.

In addition to adipose tissue surrounding the coronary arteries, intramyocardial lipid accumulation represents another manifestation of ectopic fat storage that may lead to a local adverse effect on the heart. With the use of in vivo magnetic resonance spectroscopy, higher amounts of cardiac steatosis have now been observed among individuals with impaired glucose tolerance and type-2 diabetes mellitus in comparison with individuals who are lean. It is appropriate that debate has remained as to whether cardiac steatosis is merely a marker of metabolic disturbances or alternatively contributes directly to the development of cardiac dysfunction. To try to disentangle this issue, investigators used magnetic resonance spectroscopy and found increases in intramyocardial lipid content after high-fat feeding in both wild-type mice and a mouse model of elevated triacylglyceride. Not only did the transgenic mice demonstrate more lipid accumulation, but the increase in intramyocardial lipids was not solely triglycerides. In addition, after high-fat feeding, the transgenic, but not wild-type, mice demonstrated a reduction in systolic strain as assessed by cardiac-tagged MRI strain techniques. Overall, these findings support the possibility of a causal relationship between intramyocardial lipid accumulation and cardiac dysfunction.

The possibility of local associations between a specific ectopic adipose depot and its respective organ has also been extended to thoracic periaortic fat and renal sinus fat. The
association of thoracic periaortic fat, a subtype of perivascular fat, and peripheral artery disease, is yet another example of a potential local toxic effect of an ectopic fat depot. Th Thoracic periaortic fat is hypothesized to serve as a marker of perivascular fat. Its association with peripheral arterial disease persisted despite adjustment for measures of generalized and visceral adiposity, as well as adipokines. Renal sinus fat has been postulated to affect kidney function by compressing blood vessels as they exit the kidney. Consistent with this hypothesis, renal sinus fat was found to be associated with both hypertension and chronic kidney disease even after adjustment for cardiovascular risk factors, including VAT.

Unanswered Questions and Future Directions

Although our understanding of ectopic fat depots has increased substantially in the past decade, the current body of work has uncovered areas of uncertainty. Driven by the basic science and translational literature, epidemiological studies have demonstrated associations between unique fat depots and cardiovascular disease. Further basic science and translational work will help clarify whether causal relations drive these associations. Many of the basic science studies to date have been limited to animal models. These will continue to be crucial to our understanding of ectopic fat depots, but additional investigations in human subjects will also be essential. Studies comparing and contrasting the different subtypes of ectopic fat have already highlighted important similarities and differences, and will continue to provide important insights. Further understanding of the effect of weight loss on specific fat depots will be equally important. Finally, an emerging body of work has begun to examine the genetics of body fat distribution. For example, previous work has identified 14 loci for body fat distribution independent of BMI, and a common variant of the FTO gene has been shown to be associated with the development of higher amounts of both subcutaneous and visceral adiposity.

Conclusion

Obesity will remain one of the most important worldwide public health challenges. Additional research on adipose tissue biology and ectopic fat will better identify individuals at risk for cardiovascular disease morbidity and mortality. In addition, a further understanding of the mechanisms potentially contributing to obesity-associated vascular disease may eventually lead to novel therapies. The study of ectopic fat depots and their association with metabolic risk factors and vascular disease has provided some insight in this area, but much additional work remains, and important advances are anticipated in the coming years.

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References

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