Trimming the Fat, Do We Know Where to Begin?

Satyam Sarma, MD; Benjamin D. Levine, MD

The worldwide prevalence of obese and overweight individuals has increased 3-fold during the past 30 years, from 857 million in 1980 to 2.1 billion in 2014. Once thought to be a rich world problem, rates have increased dramatically even in low- and middle-income countries with 1 in 7 obese individuals residing in China and India. As global demographic trends continue to shift toward urbanization, typified by sedentary lifestyles with easy accessibility to calorie-dense foods, rates are only expected to increase. Particularly alarming is the rapid rise in childhood obesity, portending poorly for the anticipated burdens on future healthcare systems. Obesity-related diseases have already surpassed tobacco as the largest noncommunicable cause of death worldwide.

The cause of obesity is complex and multifactorial. A combination of insulin resistance, systemic proinflammatory cytokine release, and the ability to compartmentalize fat depots within the body has further helped to delineate the relationships between fat, metabolic function, and disease risk. The development of so-called lifestyle diseases? Advances in imaging technology have improved our understanding of the relationship between body weight and health and has helped highlight the metabolic consequences of fat mass in relation to total body mass. Although body mass index is a cost-effective and simple screening tool, the sensitivity for detecting individuals with poor metabolic health and increased risk of mortality can be imprecise. In normal weight individuals, body fat percentage may be a better predictor of poor metabolic health and increased risk of mortality than total body fat mass alone.3

Recent advances in the ability to compartmentalize fat depots throughout the body (eg, epicardial, subcutaneous, perirenal, subcutaneous, etc.) have further helped to delineate the relationship between fat, metabolic function, and disease risk. The ability to distinguish subcutaneous from visceral adiposity has emphasized that not all fat behaves equally. Indeed, large-scale epidemiological studies have shown a stronger relationship between visceral fat and metabolic function, and disease risk. The association between fat, metabolic function, and disease risk is clearly present in both children and adults and spans the entire body fat mass spectrum.5-7

The causal link between visceral adiposity and cardiometabolic disease is not entirely clear but thought to be because of a combination of insulin resistance, systemic proinflammatory state from circulating adipokines, and direct toxic effects from triglyceride accumulation within organs. Although many of these relationships are likely colinear and teasing out relative associations can be difficult in observational study designs, the ability to noninvasively quantify fat stores within organs using magnetic resonance spectroscopy has spurred interest in testing and validating the lipotoxicity hypothesis.8,9 The accumulation of fat within organs interferes with normal function and under some situations can lead to complete organ failure. Nonalcoholic steato-hepatitis is now the leading cause of cirrhosis in the United States.10

In addition to the liver, the myocardium is also susceptible to ectopic fat deposition and in animal models is causally associated with significant myocardial dysfunction.11 In humans, the association between myocardial triglyceride content and cardiac dysfunction is more subtle and rarely manifests as catastrophic ventricular failure. The most common finding in patients with high levels of cardiac steatosis is decreased ventricular distensibility, increased ventricular mass, and impaired global longitudinal strain.12,13 But few cardiac steatosis studies have performed comprehensive assessments of fat depots throughout the body (eg, epicardial, subcutaneous, visceral, etc.), raising the question whether myocardial fat has any independent cardiac effects or is merely an epiphenomenon related to other fat storage sites.

The current study by Granér et al14 helps shed additional light on this dilemma. In 75 nondiabetic, noncirrhotic patients (men only) with various degrees of nonalcoholic fatty liver disease, they observed a relationship between increasing tertiles of hepatic triglyceride content and myocardial triglyceride, epi- and pericardial fat, visceral and subcutaneous fat. Patients with high hepatic triglyceride content tended to be older (47 versus 38 years), obese (body mass index, 32.2 versus 23.2 kg/m²), hypertensive, have more insulin resistance, and more likely to be smokers. Using MRI to quantify cardiac chamber size, ejection fraction, and LV diastolic filling, patients in the highest tertile had the smallest stroke volume, smallest LV end-diastolic volumes indexed to body surface area, and reduced peak diastolic filling rates. There were no differences in LV ejection fraction or mass. When analyzing correlates to decreased LV filling rates, only visceral fat and hepatic triglyceride content were associated with a decrease in peak ventricular filling rates. Myocardial triglyceride had no relation to diastolic filling. The authors conclude that visceral adipose tissue is more likely to exert systemic effects on LV diastolic performance and not myo-, epi-, or pericardial fat stores that are directly adjacent or within the heart.

Although comprehensive in their assessment of whole body adiposity and metabolic measures, a few caveats should be taken in account with regard to their findings. Assessment of diastolic dysfunction is complex and should not be limited to a single imaging modality. Measurement of flows, in particular, can be confounded by pseudonormalization of mitral inflow...
leading to a false conclusion that high levels of peak flow are because of vigorous diastolic suction and not elevated left atrial pressure. In the absence of velocity encoded or phase contrast MRI, simple volumetric and time analysis may be a suboptimal modality for assessing meaningful diastolic function.\(^1\)

In addition, the relationship between LV mass and LV end-diastolic volumes was not reported for myocardial triglyceride. Prior studies have shown a correlation between elevated myocardial triglyceride content and smaller ventricular size and increased ventricular mass, both common findings in hearts with impaired diastolic relaxation and increased diastolic stiffness. Validating or refuting this correlation in the current study would have provided an additional bit of insight into the relationship between ectopic fat and diastolic diastolic stiffness.

Regardless, the data presented by Graner suggest an important relationship between visceral adiposity and cardiac function and is consistent with observations made from epidemiological studies. In the absence of a prospective intervention study, it remains unknown whether this effect is mediated via myocardial triglyceride or via circulating factors originating from visceral fat depots. But if myocardial triglyceride content is not the mediator, then what drives its accumulation within the heart? Even in the absence of metabolic syndrome and diabetes mellitus, cardiac steatosis can develop, reaching levels observed in diabetics and likely driven by age and sedentary lifestyles.\(^3\)

To answer these questions will require high-resolution physiological studies incorporating measures of insulin resistance, changes in circulating adipokines, as well as comprehensive and thorough assessments of diastolic function. In addition, care must be taken to measure validated indicators (both imaging and serum biomarkers) of LV function because many of the cardiac manifestations of adiposity are subclinical. The relationship between fat, surrogate markers of LV function, and long-term cardiovascular disease risk is unknown.

As imaging technology becomes more sophisticated, we can answer important questions on organ function at a near molecular level. In conjunction with compelling data from population science and animal studies informing us of the relationship between adiposity and cardiovascular disease, the opportunity to stay ahead of the obesity pandemic may depend on our ability to trim the right fat depot.

**Disclosures**

None.

**References**


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