



Sylvia R. Karasu M.D.
The Gravity of Weight

Fat in All the Wrong Places

The "too, too solid flesh" of ectopic fat

Posted Nov 23, 2020



"No-body and Some-body. With the true Chronicle Historie of Elydure." Printed for J. Trundle, London, 1606.

Source: Copyright British Library Board/Bridgeman Images. Used with generous permission.

Hamlet, with his mother's egregious betrayal, laments, "O, that this too, too solid flesh would melt" (Act I, Scene 2). "He's fat and scant of breath," says Gertrude of her son (Act V, Scene 2). Poor Hamlet. Even his faithless mother calls him fat (though surprisingly, there is controversy within Shakespearean scholarship about Hamlet's corpulence). With the image of a fat, breathless Hamlet in mind, though, consider fat accumulation and specifically *ectopic fat*, i.e., fat that "deleteriously spills over" and infiltrates vital organs such as the heart, blood vessels, liver, and skeletal muscle, with its subsequent dire metabolic consequences (Hepler and Gupta, *Molecular and Cellular Endocrinology*, 2017).

Most animal species store energy in the form of white adipose tissue; in people of normal weight, it comprises 10 to 29 percent of weight and makes it "the largest organ in the body" (Kahn, *Science*, 2008). In those overweight or obese, that percentage is considerably higher. White adipose tissue "plays a key homeostatic role" not only because it stores energy but also because it can mobilize this energy quickly (Pellegrinelli et al, *Diabetologia*, 2016).

Further, white adipose tissue has a "remarkable capacity" to expand with excessive caloric intake by either *hypertrophy* (increasing size) or *hyperplasia* (increasing number). Fat cells turn over about 10 percent each year (Spalding et al, *Nature*, 2008); researchers no longer believe that fat cell number is constant throughout life (Bray and

Bouchard, *Obesity Reviews*, 2020).

Body mass index (BMI) is only a "surrogate marker" of fat, (Goossens, *Obesity Facts*, 2017); people with the same BMI may have different metabolic and cardiovascular vulnerabilities. Even waist circumference, also used as a rough measure, includes both subcutaneous fat (non-ectopic) and visceral fat (typically ectopic) (Britton and Fox, *Circulation*, 2011). More sophisticated techniques, such as ultrasound and magnetic resonance imaging (MRI), among others, are used to quantify fat within an organ.

By definition, ectopic fat is excess adipose tissue invading and encasing areas that are "not classically" associated with fat storage (Britton and Fox, 2011), i.e., triglycerides deposited "within cells of nonadipose tissue" (Ferrara et al, *Cellular Physiology*, 2019). These "anatomically distinct" depots of white adipose tissue are "distinct mini-organs" (Hepler and Gupta, 2017). Why does ectopic fat accumulate?

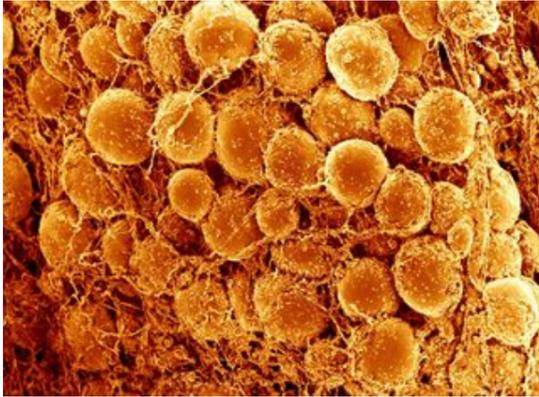
Adipose tissue is "profoundly impacted by chronic overfeeding" (Bray and Bouchard, 2020). For an extraordinarily comprehensive review of the effects of the biology of overfeeding, see Bray and Bouchard, 2020. Ultimately, adipocytes (fat cells) become "exhausted" (Hepler and Gupta, 2017). One mechanism



Advertisement for a slimming cure, c. 1895. Both men and women are at risk for developing ectopic fat with increasing obesity. French School, Private Collection.

Source: Bridgeman Images. Photo credit: Roger-Viollet, Paris. Used with permission.

hypothesized is that since the storage capacity of subcutaneous adipose cells is not infinite, it reaches its limit in this state of positive energy balance. Ectopic fat, therefore, “may result from the failure of subcutaneous adipose tissue to act as a metabolic sink” (Britton and Fox, 2011), creating a "mismatch" between "storage demands" from excess calories and "storage space" that is determined by how much adipose tissue can expand (Carobbio et al, in Engin and Engin, eds, *Obesity and Lipotoxicity, Advances in Experimental Medicine and Biology*, 2017). In humans, there is considerable biological variability to overfeeding (Bray and Bouchard, 2020), and even fat cell size and number (Mejhert and Rydén, *Current Opinion in Pharmacology*, 2020).



Adipocytes (fat cells), electron micrograph. Source: Wellcome Trust Collection. Attribution 4.0 International. Contributors: David Gregory & Debbie Marshall.

It still remains unknown how size "mechanistically initiates and drives" alterations in white adipose tissue (Mejhert and Rydén, 2020), and even "why the body can store subcutaneous fat abundantly when overeating but nevertheless fails to store all of it..." leading to ectopic accumulation (De Munck et al, *European Journal of Clinical Nutrition*, 2020).

What determines this infiltration into organs, though, depends on genetics and environmental factors, including age, sex, race, nutrition, history of smoking, etc. There is even the suggestion that those who eat more frequently show a greater tendency to develop ectopic fat than those who eat less frequently (Bray and Bouchard, 2020).

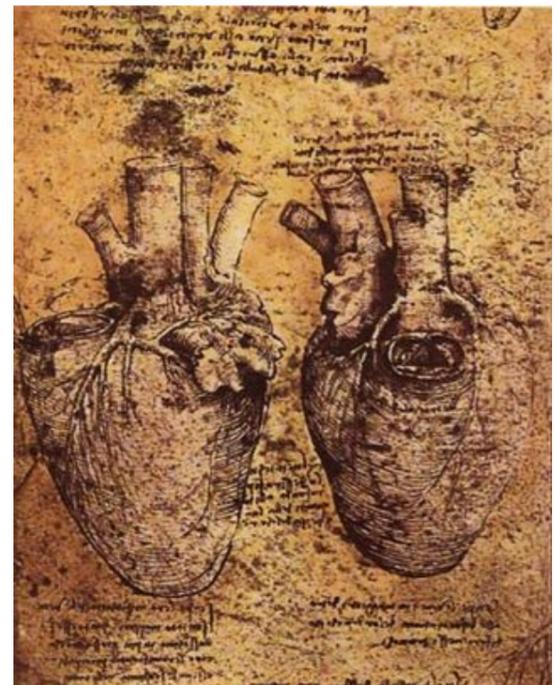
Ectopic visceral fat is highly vascularized and more metabolically active (with its pro-inflammatory and immune cells), than subcutaneous fat (Mejhert and Rydén, 2020). Most importantly, it is particularly toxic because lipids drain directly into the portal circulation and affect the functioning of the liver (Hepler and Gupta, 2017; Bosy-Westphal et al, *European Journal of Clinical Nutrition*, 2019). Increased fat in the liver is even more detrimental than ectopic fat in other areas (Bray and Bouchard, 2020).



Peter Paul Rubens, "Prometheus Bound," 1611-12. Philadelphia Museum of Art. The liver is particularly vulnerable to ectopic fat accumulation. Prometheus's liver was eaten nightly by an eagle, sent by Zeus to punish him for giving fire to humans. Source: Wikimedia Commons/Public Domain. Source/photographer: The Yorck Project, 2002.

In fact, the most common cause of chronic liver disease in the U.S. is nonalcoholic fatty liver disease (NAFLD), defined as the presence of more than 5 percent fat accumulation (steatosis). This is the "hepatic manifestation of the metabolic syndrome"

(Ferarra et al, 2019; Rhee, *Endocrinology and Metabolism*, 2019). In the U.S., the prevalence of NAFLD is 30 to 40 percent among adults, and many are diagnosed incidentally by abnormal liver enzymes since patients can be asymptomatic (Sharma and John, *NCBI Bookshelf*, 2020). Prevalence rates are even higher (up to 70 percent), depending on the ethnic group studied and diagnostic methods used (Rhee, 2019). Ultimately, patients can develop hepatitis that can progress to fibrosis, cirrhosis, and even hepatocellular carcinoma (Sharma and John, 2020). Further, there is also now "strong epidemiological evidence" that NAFLD is a risk factor for type 2 diabetes (Rhee, 2019), and those with NAFLD and type 2 diabetes have an increased risk for these complications (Rhee, 2019).



Leonardo da Vinci's "Heart and its Blood Vessels," late 15th century from Biblioteca Ambrosiana. Ectopic fat can surround and infiltrate the heart muscle and its blood vessels and lead to conduction abnormalities. Source: Wikimedia Commons/Public Domain. Source: Web Gallery of Art

When adipose tissue infiltrates organs, such as the liver and muscle that are fundamental to glucose and insulin metabolism, systemic “metabolic derangements”(e.g. insulin resistance, chronic inflammation) can occur (Britton and Fox, 2011; Hepler and Gupta, 2017), resulting in "metabolic inflexibility" and a build-up of "lipotoxic metabolites" (Trouwborst et al, *Frontiers in Nutrition*, 2018).

Further, ectopic fat can create oxidative stress and mitochondrial dysfunction (Ferrara et al, 2019). Those deposits that surround the heart and blood vessels can have local effects as well and lead to cardiac dysfunction (Britton and Fox, 2011), including atrial fibrillation (Ferrara et al, 2019; Piché and Poirier, *Expert Review of Endocrinology & Metabolism*, 2018).



The Reibekuchen King by German artist Christian Rohlf, 1909-10. With massive obesity, ectopic adipose tissue infiltrates the body's organs and creates metabolic dysfunction. Source: Photo copyright, Christie's Images/Bridgeman Images. Used with permission.

Bottom line: Ectopic fat is fat that deleteriously spills over in all the wrong places—encasing and infiltrating organs such as the heart, liver, blood vessels, and skeletal muscle.

Developing in the context of excessive caloric intake, i.e., that “too, too solid flesh” of overweight and obesity, it reflects a mismatch between storage demands and the storage capacity of white adipose tissue, creating a lipotoxic state and metabolic havoc, including insulin resistance, inflammation, chronic liver disease, cardiac dysfunction, and type 2 diabetes.



Anatomical illustration of man and woman holding their internal organs, c. 1700, Persian School, "The medicine of Akbar." Source: Prismatic Pictures. Bridgeman Images. Used with permission.

Note: The focus of my blog is white adipose tissue and ectopic fat accumulation and not brown or beige adipose tissue. (For that discussion, [see my blog](#))

About the Author



[Sylvia R. Karasu, M.D.](#), is a clinical professor of psychiatry at Weill Cornell Medical College and the senior author of *The Gravity of Weight*.

Online: [my own website](#)