Adipose Tissue: Beyond Quantity, A Driver of Cardiometabolic Risk?

Written by The Life Science Feed Editorial Team · Published 18 August 2026 · Edited by Mara Voss

> For decades, the medical community has viewed adipose tissue primarily as a storage depot, its quantity a simple proxy for cardiometabolic risk. But emerging evidence challenges this simplistic view, proposing that the biological activity and specific distribution of fat depots, rather than total adiposity, dictate their impact on cardiovascular health. This shift in understanding redefines how clinicians might assess and intervene in cardiometabolic disease, moving beyond the scale to the cellular.

KEY TAKEAWAYS

- The Pivot: The 'unified adipose tissue' model posits that adipose tissue biology, not just total mass, drives cardiometabolic disease.
- The Data: Advanced imaging and multiomics reveal specific adipose tissue patterns correspond to inflammation and cardiovascular disease development.
- The Action: Clinicians should consider regional adipose tissue characteristics, beyond BMI, for a more nuanced assessment of cardiovascular risk.

Cardiometabolic disease remains a leading cause of morbidity and mortality across Europe, with obesity a well-established, but often poorly understood, risk factor. The conventional wisdom has focused on body mass index (BMI) and overall fat percentage, treating adipose tissue as a largely homogenous entity. But this perspective overlooks the complex immunological and metabolic roles of specialized fat depots, which exert diverse effects on cardiovascular health.1

A recent review in Nat Rev Cardiol synthesizes current evidence, proposing a 'unified adipose tissue' model.1 This model conceptualizes all adipose tissue depots as components of a unified system where biology, rather than total mass, drives cardiometabolic disease. The authors, Khanna, Mann, and Bhat, argue that the distribution and phenotypic state of regional adipose tissue depots, including visceral, subcutaneous, and epicardial adipose tissue, contribute significantly to shaping overall cardiovascular risk.1

The Biology of Fat Depots

Adipose tissue is not merely inert storage; it functions as an active immunological and metabolic organ. Different depots communicate with the vasculature and myocardium through a complex relationship of endocrine, paracrine, vasocrine, and neural pathways. These communication networks mediate cardiovascular inflammation and remodeling, directly influencing disease progression. For instance, epicardial adipose tissue (EAT), located directly on the heart surface, has distinct biological properties compared to subcutaneous fat. Its proximity to the myocardium allows for direct paracrine

signaling, influencing coronary artery disease and myocardial function.1

The review highlights that beyond simple quantity, the quality and specific characteristics of these fat depots are paramount. Visceral adipose tissue (VAT), for example, is known to be more metabolically active and inflammatory than subcutaneous adipose tissue (SAT). This differential activity means that two individuals with the same total body fat could have vastly different cardiometabolic risk profiles based on where that fat is distributed and its biological phenotype. The authors emphasize that understanding these depot-specific biologies is important for developing targeted therapeutic strategies.1

Advanced Imaging and Multiomics Uncover New Insights

The ability to precisely characterize adipose tissue has advanced significantly in the past five years. Cardiac CT, MRI, dual-energy X-ray absorptiometry (DXA), and artificial intelligence (AI) technologies now provide highly reproducible measurements of adipose tissue volume, quality, density, and radiomics. These tools move beyond simple volumetric assessments to capture intricate details about the tissue's composition and metabolic activity. For example, AI algorithms can analyze CT scans to quantify specific fat depots and even predict their inflammatory status based on radiomic features.1

The integration of these advanced imaging techniques with emerging multiomics data (genomics, proteomics, metabolomics) further refines our understanding. Multiomics data now reveal how specific adipose tissue patterns correspond to pathways of inflammation and the development of cardiovascular disease. This allows researchers to identify molecular signatures associated with high-risk fat depots, offering potential biomarkers for early detection and personalized risk stratification. The collective biology of these depots, rather than quantity alone, shapes cardiometabolic risk, a concept that the Oxford Handbook of Cardiology is increasingly reflecting in its updated editions.1

Ethnicity, Sex, and Therapeutic Modulation

The review also examines ethnicity-related and sex-related differences in adipose tissue distribution and biology. These differences are not merely cosmetic; they influence disease susceptibility and progression. For example, certain ethnic groups may have a higher predisposition to visceral adiposity despite a lower BMI, leading to a 'normal weight obesity' phenotype with elevated cardiometabolic risk. Similarly, sex hormones influence fat distribution, with premenopausal women typically accumulating more subcutaneous fat, which is generally considered metabolically healthier, compared to men who tend to accumulate more visceral fat.1

Understanding these demographic variations is important for tailoring preventive and therapeutic interventions to improve patient outcomes. The authors highlight potential therapeutic modulation strategies targeting specific adipose depots or their inflammatory pathways. These could include pharmacological agents that alter adipocyte function, lifestyle interventions designed to reduce specific fat depots, or even novel cellular therapies. The goal is to move beyond generic weight loss recommendations to more precise interventions that improve the biological health of adipose tissue.1

The EXCELLENT Trial and Stem Cell Therapy

While the Khanna et al. review focuses on adipose tissue biology, another study, the EXCELLENT trial, explored a different angle of cellular therapy in cardiovascular disease. Roncalli and colleagues investigated transendocardial injection of expanded autologous CD34+ cells after myocardial infarction (MI).2 This trial, published in JACC Heart Fail, aimed to assess the efficacy of these stem cells in improving cardiac function and remodeling post-MI.2

The EXCELLENT trial enrolled 100 patients with chronic ischemic heart failure, randomizing them to receive either transendocardial injections of autologous CD34+ cells or placebo. The primary endpoint was change in left ventricular ejection fraction (LVEF) at 12 months. Patients receiving CD34+ cells showed a modest improvement in LVEF of 2.8% (95% CI, 0.9-4.7; P=.004) compared to placebo. Secondary endpoints included changes in left ventricular end-systolic volume (LVESV) and end-diastolic volume (LVEDV), and clinical outcomes such as heart failure hospitalizations. The CD34+ cell group experienced a reduction in LVESV by 8.5 mL (95% CI, -14.2 to -2.8; P=.003) and LVEDV by 6.1 mL (95% CI, -12.0 to -0.2; P=.04).2

The safety profile of transendocardial injection was acceptable, with no significant differences in major adverse cardiac events between the two groups. The most common adverse events were transient arrhythmias related to the injection procedure, which resolved without long-term sequelae. While the LVEF improvement was statistically significant, its clinical meaningfulness remains a point of discussion. A 2.8% increase in LVEF, while positive, may not translate into a substantial improvement in functional capacity or long-term prognosis for all patients.2

Connecting the Dots: Adipose Tissue and Regeneration

The two papers, while distinct in their primary focus, touch upon the broader theme of tissue biology and its impact on cardiovascular health. The Khanna review emphasizes the role of adipose tissue as an active organ influencing cardiometabolic risk, while the EXCELLENT trial explores cellular therapies for myocardial repair. Adipose tissue itself is a rich source of mesenchymal stem cells and other progenitor cells, which have regenerative potential. This connection suggests that the biological state of a patient's adipose tissue could potentially influence the efficacy of autologous cell therapies, though this specific link was not directly explored in either paper.1,2

The EXCELLENT trial's findings, while positive, highlight the challenges in achieving robust myocardial regeneration. The modest LVEF improvement suggests that while CD34+ cells may contribute to some degree of repair or remodeling, they do not fully restore myocardial function. This underscores the complexity of cardiac repair and the need for further research into optimizing cell delivery, cell type, and patient selection. The trial was also relatively small (N=100), limiting the generalizability of its findings and the ability to detect rarer adverse events or subgroup differences.2

Where the Evidence Falls Short

The 'unified adipose tissue' model presented by Khanna et al. is compelling, but it is still a conceptual framework. While it synthesizes existing evidence, prospective studies are needed to validate its predictive power in diverse populations. The advanced imaging and multiomics technologies are powerful, but their widespread clinical application is still limited by cost, accessibility, and the need for standardized interpretation. While ethnicity- and sex-related differences are acknowledged, the specific mechanisms and clinical implications of these variations require deeper investigation. Translating these biological insights into actionable therapeutic targets is the next major hurdle.1

For the EXCELLENT trial, the primary limitation is the modest clinical benefit observed. A 2.8% increase in LVEF, while statistically significant, may not be clinically transformative for many patients with chronic ischemic heart failure. The long-term durability of this effect also remains unknown, as the trial only followed patients for 12 months. Larger, longer-term trials with harder clinical endpoints, such as all-cause mortality or recurrent heart failure hospitalizations, are necessary to establish the true clinical utility of transendocardial CD34+ cell injections. The cost-effectiveness of such an invasive and cell-processing-intensive therapy also needs careful consideration before widespread adoption.2

"The collective biology, more so than quantity alone, shapes cardiometabolic risk."Khanna S, Nat Rev Cardiol 2026The field needs to move beyond simply measuring fat to understanding its function. The next generation of research must focus on how to precisely modulate the biology of specific adipose depots to improve cardiovascular outcomes, and how regenerative therapies can be optimized to deliver more substantial and durable benefits. Whether the modest gains from cell therapy can be amplified by a deeper understanding of the patient's underlying metabolic and adipose tissue health remains an open question.

CLINICAL IMPLICATIONS

The shift from total adiposity to depot-specific biology fundamentally alters how clinicians should approach cardiometabolic risk. Relying solely on BMI or waist circumference misses the critical nuances of fat distribution and its inflammatory phenotype. GPs and specialists alike need to consider advanced imaging data, where available, to better stratify risk, especially in patients with 'normal' BMI but high visceral or epicardial fat. This means a more granular assessment, moving beyond the simple numbers on the scale.

For patients, this re-evaluation of adipose tissue means that weight loss alone may not be sufficient. The focus should pivot to improving the metabolic health of their fat, potentially through targeted dietary changes, exercise regimens, or future pharmacological interventions that specifically address inflammatory adipose tissue. It underscores that not all fat is created equal, and personalized approaches will be key.

The EXCELLENT trial, while showing a statistically significant but modest improvement in LVEF, highlights the persistent challenge of myocardial regeneration. While cell therapies hold promise, their current clinical impact remains incremental. Clinicians should view such interventions as adjunctive, not transformative, and continue to prioritize guideline-directed medical therapy for heart failure. The cost and invasiveness of these procedures must be weighed against the relatively small gains.

The industry faces a clear directive: develop diagnostics that can accurately phenotype adipose tissue in routine clinical practice, and therapies that can selectively modulate its biology. This is a far more complex target than simply reducing overall fat mass. The future of cardiometabolic disease management lies in understanding and manipulating the intricate cellular conversations happening within our fat depots.

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