

## **Study Finds Weight Loss Wipes Out Senescent Fat Cells but Leaves Immune Scars**

Researchers utilized next-generation assays to investigate the regulatory factors, cell types, and molecular events involved in [human adipose tissue](#) (AT) remodeling. Their landmark study provides the most detailed view yet into how fat tissue transforms during obesity and weight loss.

Study findings reveal that obesity induces cellular senescence, inflammation, and structural stress within fat, which are only partially reversed by [weight loss](#). Notably, senescence reversal was selective, occurring in metabolic adipocytes, vascular cells, and precursors where p21-positive senescent cells were nearly eliminated, but largely persistent in immune cells. In combination with the 171,247-cell strong atlas, these findings provide a revolutionary understanding of fat tissue plasticity, representing the first step towards novel therapeutic directions that may finally overcome obesity's notorious capacity to bounce back.



### **Study**

The present study aims to address this knowledge gap and progress our war on obesity by deciphering the cellular, molecular, and spatial changes that occur in human AT during [obesity](#) and after weight loss.

Study samples (subcutaneous abdominal AT) were obtained from morbidly obese patients (BMI > 35 kg/m<sup>2</sup>; n = 25; age = 20–70 yrs) and healthy controls (BMI < 26 kg/m<sup>2</sup>) intra-operatively via laparoscopic [bariatric surgery](#). Follow-up samples were collected five months later for comparative assays. All samples were subjected to single-nucleus RNA sequencing (snRNA-seq) using the Illumina NextSeq2000 platform.

In brief, the study profiled ~100,000 nuclei from fresh biopsies and integrated the resultant sequences with 50,000 additional nuclei from the largest human fat tissue atlas to date. To supplement this [single-cell data atlas](#), the 10x Genomics' Xenium platform was leveraged to conduct spatial transcriptomics on over 25,000 cells from equivalent cohorts, allowing researchers to observe differences in tissue-specific cell states.

Simultaneously, formalin-fixed paraffin-embedded (FFPE) AT samples were subjected to 5 µm sectioning, 4',6-diamidino-2-phenylindole (DAPI) staining, and [in situ hybridization assays](#), allowing researchers to both carry out nuclear identification and measure gene activity directly within intact tissue architecture.

Finally, the study used pathway enrichment (MSigDB), [differential expression](#), transcription factor inference, and spatial niche modeling assays to elucidate the movement, activity patterns, and remodellings of metabolic, immune, vascular, and progenitor cell populations.

## **Results**

### ***Weight loss selectively reverses senescence in metabolic, vascular, and precursor cells***

[Metabolic adipocytes](#), precursor cells, and vascular cells of patients with obesity were found to express senescence-associated secretory phenotype (SASP) genes and other markers of cellular senescence. These cells contribute to fibrosis, immune signaling, and local tissue stress.

Notably, following weight loss (bariatric surgery), the fraction of "[stressed](#)" adipocytes (AD3) was observed to decrease dramatically (from 55% to 14%;  $P < 0.0001$ ), and p21-positive senescent cells were nearly eliminated in these lineages. However, senescence persisted in immune cells (macrophages), suggesting only partial and cell-type-specific rejuvenation of the adipose niche.

### ***Immune cells retain inflammatory programming post-weight loss***

While the infiltration of [lipid-associated macrophages](#) (LAMs) was observed to decrease following weight loss, these LAMs retained inflammatory signature (TREM1 and TLR2) expression, indicating transcriptional memory that may predispose to metabolic dysfunction and potentially explain obesity's frequent reappearance.

### ***Weight loss reduces structural tissue stress and fibrosis***

Weight loss was observed to substantially downregulate the expression of genes (e.g., LOX, ACTA2, and VGLL3) involved in fibrosis and [cytoskeletal tension](#), resulting in reduced adipocyte stiffness and inflammation.

### ***Spatial mapping reveals stress niches adjacent to immune hotspots***

The study identified five functional tissue niches: adipocyte, vascular, stress, arterial, and stem-like zones. Stressed cells formed distinct "[stress niches](#)" adjacent to immune-enriched arterial zones, indicating microenvironments of obesity-caused damage with delayed recovery. Several stress-associated factors (THBS1, NAMPT, AREG) were found to be enriched in obesity and reversed by weight loss ( $P < 0.05$ ), highlighting them as potential therapeutic targets.

## **Conclusion**

This study marks a prominent leap in scientific understanding of adipose tissue biology, highlighting that while [weight loss](#) can partially and selectively reverse the cellular damage inflicted by obesity (reducing inflammation, senescence in specific lineages, and tissue stress), some immune and metabolic programs retain obesity-associated signatures, potentially explaining the stubborn tendency for weight to return.

The findings highlight fat as a complex, adaptive organ exhibiting cell-type-specific memory, suggesting that future interventions targeting unresolved senescence (e.g., in macrophages) or niche-specific [stress signals](#) (e.g., THBS1/NAMPT) may improve long-term outcomes.

## **Source:**

<https://www.news-medical.net/news/20250710/Weight-loss-wipes-out-senescent-fat-cells-but-leaves-immune-scars-study-finds.aspx>