Advancements in Health Research

Advancements in Health Research 2026; 3:143
doi:10.4081/ahr.2026.143

From symptom control to biological restoration: the expanding role of microfragmented adipose tissue in pain and regenerative medicine

Giustino Varrassi,[1,2] Pierfrancesco Dauri[3]

[1]Fondazione Paolo Procacci, Rome, Italy; [2]College of Medicine, Baghdad University, Baghdad, Iraq; [3]Department of Pain Management, Pertini Hospital, Rome, Italy

Key words: adipose tissue; regenerative medicine; mesenchymal stem cells; chronic pain; osteoarthritis; inflammation; angiogenesis

Correspondence to: Giustino Varrassi, Fondazione Paolo Procacci, Via Tacito 7, 00193 Rome, Italy. E-mail: giuvarr@gmail.com

Introduction

The past two decades have witnessed a profound conceptual evolution in medicine, moving from a predominantly symptom-oriented approach toward strategies aimed at restoring tissue integrity and biological function. Nowhere is this shift more evident than in the management of chronic pain and degenerative musculoskeletal disorders, where conventional pharmacological and interventional treatments frequently fail to address the underlying pathophysiological mechanisms. In this context, regenerative medicine has emerged as a compelling paradigm, offering the possibility of modifying disease processes rather than merely attenuating symptoms.

Among the various regenerative approaches, adipose-derived therapies have gained increasing attention due to their accessibility, relative safety, and biological richness. Micro-fragmented adipose tissue (MFAT), particularly as processed through the Lipogems® system, represents a distinctive strategy that preserves the native stromal vascular niche while complying with regulatory definitions of minimal manipulation.[1] This editorial aims to contextualize the emerging role of MFAT within the broader landscape of pain medicine and regenerative therapeutics, highlighting its biological rationale, current clinical evidence, limitations, and future directions.

The biological rationale: beyond cells, toward a functional microenvironment

The therapeutic promise of MFAT lies not merely in the presence of mesenchymal stromal cells (MSCs), but in the preservation of a complex and functional microenvironment. Adipose tissue is a heterogeneous organ composed of adipocytes, endothelial cells, immune cells, pericytes, and extracellular matrix (ECM) components that together form a dynamic regenerative niche. Unlike enzymatically derived stromal vascular fraction (SVF), which disrupts tissue architecture, MFAT retains structural integrity, enabling sustained cell-cell and cell-matrix interactions. This preservation is not trivial. Increasing evidence suggests that the regenerative capacity of adipose-derived products is primarily mediated through paracrine signaling rather than direct cellular differentiation. MSCs and pericytes secrete a wide array of bioactive molecules, including cytokines, growth factors, and extracellular vesicles, which modulate inflammation, promote angiogenesis, and orchestrate tissue repair. In particular, the ability to shift the local microenvironment from a pro-inflammatory to an anti-inflammatory state is highly relevant in chronic pain conditions, where persistent low-grade inflammation and neuroimmune dysregulation play central roles.

Furthermore, the retention of perivascular niches within MFAT enhances its biological activity. Pericytes, increasingly recognized as progenitors of MSCs, contribute to vascular stability, angiogenesis, and immunomodulation.[2] Their presence within intact microvascular structures allows for context-dependent activation in response to tissue injury, potentially amplifying regenerative responses.

Inflammation and pain: a converging target

Chronic pain is now widely understood as a multidimensional condition involving complex interactions between peripheral tissues, the nervous system, and immune pathways.[3] Inflammatory mediators such as interleukin-1β and tumor necrosis factor-α not only drive tissue degeneration but also sensitize nociceptors, contributing to pain persistence and chronification.

MFAT directly addresses this pathophysiological axis. Through the secretion of anti-inflammatory cytokines and the modulation of immune cell behavior, particularly macrophage polarization toward an M2 phenotype, MFAT may attenuate both structural and neuroinflammatory processes. This dual action positions MFAT as a potentially valuable tool in the management of mixed pain states, where nociceptive, neuropathic, and nociplastic mechanisms coexist.[4]

Importantly, the anti-inflammatory effects of MFAT are complemented by its capacity to modulate extracellular matrix turnover and support tissue remodeling. By regulating matrix metalloproteinases and their inhibitors, MFAT contributes to balanced tissue repair, reducing fibrosis and promoting functional recovery.

Angiogenesis and tissue regeneration: rebuilding the microcirculation

Effective tissue repair requires adequate vascularization. Impaired microcirculation is a hallmark of many degenerative conditions, limiting oxygen and nutrient delivery while perpetuating a hostile microenvironment. MFAT-derived factors, including vascular endothelial growth factor and hepatocyte growth factor, stimulate endothelial cell proliferation and capillary formation, thereby enhancing tissue perfusion.

The preservation of microvascular architecture within MFAT further supports angiogenesis by maintaining pericyte-endothelial interactions essential for vessel maturation and stability. This integrated approach to vascular regeneration not only facilitates structural repair but may also reduce ischemia-related nociceptive signaling, thereby contributing to pain relief.

Clinical applications: evidence and emerging indications

Musculoskeletal disorders

The most robust clinical evidence for MFAT pertains to osteoarthritis, where multiple studies have reported improvements in pain and function following intra-articular injection.[5] While these findings are encouraging, it is important to recognize that the majority of available studies are observational, with limited randomized controlled trials. Comparative data suggest that MFAT may provide longer-lasting benefits than corticosteroids or hyaluronic acid in some contexts, although definitive conclusions are constrained by methodological heterogeneity.

Tendinopathies and sports medicine

MFAT has also been investigated in chronic tendinopathies and sports-related injuries.[6] Randomized and mechanistic studies indicate potential benefits in tendon healing and rotator cuff repair, likely mediated by enhanced collagen synthesis and modulation of local inflammation. However, evidence for its use in muscle injuries and ligament repair remains limited, highlighting the need for targeted research in these areas.

Beyond structural repair: chronic pain and other indications

The application of MFAT in chronic pain conditions such as low back pain, facet arthropathy, and neuropathic pain remains largely exploratory. While biological plausibility is strong, supported by its immunomodulatory and neuroactive properties, robust clinical evidence is still lacking. Similarly, emerging applications in wound healing, reconstructive surgery, and urology are supported by early clinical studies but require further validation.

Safety and regulatory considerations

One of the key advantages of MFAT, particularly when processed through systems such as Lipogems®, is its favorable safety profile. Reported adverse events are generally minor and related to the harvesting procedure. Importantly, the technology aligns with regulatory frameworks governing minimally manipulated tissues, such as the U.S. Food and Drug Administration's HCT/P 361 pathway and corresponding European guidelines. This facilitates clinical translation and distinguishes MFAT from more extensively manipulated cell therapies that face greater regulatory hurdles.

Limitations of current evidence

Despite its promise, the current evidence base for MFAT is characterized by several limitations. Study designs are often heterogeneous, with small sample sizes and short follow-up durations. Variability in harvesting, processing, and injection techniques further complicates comparisons across studies. The potential influence of placebo effects, particularly in pain research, cannot be overlooked. Moreover, while paracrine mechanisms are widely accepted, the precise molecular pathways underlying MFAT's therapeutic effects remain incompletely understood.

Future directions: toward precision regenerative medicine

The future of MFAT lies in its integration into a broader precision medicine framework. Advances in biomarker identification, imaging, and clinical phenotyping may enable more accurate patient selection and personalized treatment strategies. Combination therapies, incorporating platelet-rich plasma, biomaterials, or gene-based approaches, hold the potential to enhance regenerative outcomes.

Artificial intelligence and digital health technologies may further transform this field by enabling predictive modeling, treatment optimization, and real-time monitoring of therapeutic responses. However, these innovations must be accompanied by rigorous clinical validation.

Critically, the field requires high-quality randomized controlled trials with standardized protocols and long-term follow-up to establish the efficacy, safety, and optimal indications of MFAT. Without such evidence, its integration into mainstream clinical practice will remain limited.

Conclusions

Microfragmented adipose tissue represents a promising convergence of biological plausibility and clinical applicability in regenerative medicine. By addressing key mechanisms underlying chronic pain and tissue degeneration, namely inflammation, impaired vascularization, and dysfunctional repair, MFAT offers a novel therapeutic approach that extends beyond traditional symptom control.

However, enthusiasm must be tempered by scientific rigor. The transition from promising innovation to established therapy will depend on the generation of robust, high-quality evidence and the development of standardized, reproducible methodologies. As the field evolves, MFAT has the potential to redefine the management of chronic pain and degenerative disorders, bridging the gap between regenerative biology and clinical therapeutics.

References

1. Van Tran Y, Van Pham P, Encinas MAN, et al. Regenerative medicine and microfragmented adipose tissue: the emerging role of Lipogems® in pain management and tissue repair. Preprints 2026, 2026040866.
2. Vezzani B, Shaw I, Lesme H, Yong L, et al. Higher pericyte content and secretory activity of microfragmented human adipose tissue compared to enzymatically derived stromal vascular fraction. Stem Cells Transl Med 2018;7:876-86.
3. Moncada MAA, Tamayo MAN, Encinas MAN, et al. Immuno-inflammatory mechanisms in the chronification of pain. Pain Ther 2026;15:443-64.
4. Varrassi G, Farì G, Narvaez Tamayo MA, et al. Mixed pain: clinical practice recommendations. Front Med (Lausanne) 2025;12:1659490.
5. Hu X, Zhang Z, Zhang W, et al. Efficacy and safety of microfragmented adipose tissue combined with knee arthroscopy in the treatment of knee osteoarthritis: a systematic review. J Orthop Surg Res 2025;20:646.
6. Senesi L, De Francesco F, Marchesini A, et al. Efficacy of adipose-derived mesenchymal stem cells and stromal vascular fraction alone and combined to biomaterials in tendinopathy or tendon injury: systematic review of current concepts. Medicina (Kaunas) 2023;59:273.

Received: 22 April 2026; Accepted: 23 April 2026.

Contributions: both authors meet the criteria for authorship, have approved the final version of the manuscript, and agree to be accountable for all aspects of the work.

Acknowledgments: the authors wish to express their gratitude to the Fondazione Paolo Procacci for the generous and sustained support throughout all phases of the publication process. The Fondazione's steadfast commitment to advancing scientific research and promoting academic excellence has been pivotal in enabling the conception, development, refinement, and dissemination of this work.