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NOVEL APPROACHES IN OBESITY TREATMENT: THE PROMISE OF GENE THERAPIES

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ABSTRACT

Introduction and Purpose: Obesity constitutes a significant global public health concern driven by multifactorial interactions among genetic, metabolic, and environmental determinants [2, 7, 13, 28]. Conventional interventions—including lifestyle modification, pharmacotherapy, and bariatric procedures—frequently provide only limited or temporary benefits [2, 21]. This review evaluates emerging gene-based therapeutic strategies designed to target the molecular pathways responsible for obesity development and progression.

Current State of Knowledge: Preclinical animal studies utilizing adeno-associated virus (AAV) vectors have demonstrated effective adipose-tissue-specific gene delivery, resulting in enhanced thermogenesis, improved insulin sensitivity, and measurable reductions in adiposity [8, 10, 12, 16, 26]. Key metabolic regulators, such as fibroblast growth factor 21 (FGF21), uncoupling protein 1 (UCP1), and elements of the leptin–melanocortin axis, have shown promising modulation in experimental models [4, 8, 9, 22,32]. Furthermore, adipose-derived mesenchymal stem cells are being explored as potential vehicles for targeted gene delivery, although these approaches remain in early developmental phases [14]. Clinically, the most advanced gene-based interventions include RNA interference (RNAi) platforms—particularly modulators of pathways such as ALK7 or INHBE—which are currently undergoing evaluation for obesity management [23, 31].

Summary: While gene therapy applications for obesity remain primarily experimental, emerging evidence underscores their potential to address fundamental metabolic dysfunction rather than merely mitigate clinical manifestations [8, 18, 24]. Advancements in vector precision, tissue-targeted delivery, and long-term safety evaluation will be essential for future translation into clinical practice [10, 11, 26]

KEYWORDS

Obesity, Gene Therapy, AAV Vectors, RNA Interference, Metabolic Regulation, Precision Medicine

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Introduction

Obesity has emerged as one of the most critical public health challenges of the 21st century, with global prevalence rising at an unprecedented rate across all age groups and socioeconomic settings. Recent epidemiological analyses indicate that obesity now affects more than one billion individuals worldwide, driven by complex interactions among genetic predisposition, environmental exposure, endocrine regulation, and metabolic programming [2, 7, 13, 28]. Beyond its direct health burden, obesity substantially increases the risk of type 2 diabetes, cardiovascular disease, nonalcoholic fatty liver disease (NAFLD), and multiple cancer types, contributing to significant morbidity, mortality, and healthcare expenditure [3, 25]. Despite decades of research, conventional treatment strategies—including lifestyle intervention, pharmacotherapy, and bariatric surgery—often yield limited or transient results, with high rates of weight regain and variable long-term efficacy [2, 21]. This therapeutic gap underscores the urgent need for novel approaches targeting the underlying biological mechanisms driving excess adiposity.

Over the past decade, advances in molecular biology, gene editing, and vector engineering have opened new possibilities for modulating metabolic pathways implicated in obesity pathogenesis. Increasing evidence demonstrates that adipose tissue is a dynamic endocrine organ, capable of regulating energy expenditure, systemic glucose homeostasis, and inflammation through complex networks of adipokines, transcriptional programs, and intercellular communication [9, 20, 27]. Among the pathways under exploration, fibroblast growth factor 21 (FGF21), uncoupling protein 1 (UCP1), leptin–melanocortin signaling, and Hedgehog-related regulatory cascades have emerged as promising targets for genetic modulation aimed at enhancing thermogenesis, improving insulin sensitivity, and reducing fat mass [4, 8, 9, 17, 22, 30,32].

Concurrently, vector development has progressed rapidly. Recombinant adeno-associated viruses (AAVs) have become the leading platform for gene delivery due to their favorable safety profile, long-term

expression potential, and modifiable tissue tropism. Studies utilizing AAV serotypes tailored for adipose tissue—such as rAAV8 or next-generation adipose-tropic variants—demonstrate efficient transduction, metabolic benefits, and reversible obesity phenotypes in murine models [10–12, 16, 26]. Complementary strategies employ adipose-derived mesenchymal stem cells as cellular carriers capable of homing to inflamed or expanding adipose depots and delivering therapeutic transgenes with high specificity [14].

While most gene-based interventions remain in the preclinical phase, clinical translation is beginning to accelerate. RNA interference (RNAi) technologies and antisense oligonucleotide (ASO) platforms targeting regulators such as ALK7 and INHBE are currently being evaluated for their capacity to reduce adiposity and enhance metabolic health, marking a significant shift toward mechanistically driven obesity therapies [1, 23, 31]. These developments reflect a broader transition from symptom-oriented treatment to pathway-directed molecular precision medicine.

Given these advancements, gene therapy represents a transformative and increasingly realistic frontier in obesity management. However, its clinical application requires careful consideration of tissue-specific delivery, vector immunogenicity, durability of response, and long-term safety outcomes. This review synthesizes current evidence on gene-based approaches to obesity, highlighting breakthroughs in vector design, metabolic pathway manipulation, and therapeutic efficacy, as well as outlining key challenges and future research directions essential for successful translation into clinical practice.

Methodology

This review was conducted to synthesize current evidence on gene-based therapeutic strategies targeting molecular mechanisms underlying obesity. A structured approach was applied to ensure comprehensive coverage of relevant literature while maintaining the flexibility appropriate for an emerging and rapidly evolving research field.

Study Design

A **narrative review design** was used, supplemented with elements of **scoping review methodology** to capture the breadth of available preclinical and early clinical data. This design was selected due to the heterogeneity of study types, which included animal experiments, vector engineering studies, mechanistic investigations, and early-phase clinical research.

Data Sources and Search Strategy

A comprehensive literature search was performed across major biomedical databases:

- **PubMed/MEDLINE**
- **Scopus**
- **Web of Science**
- **Google Scholar** (supplementary search for gray literature and recent publications)

The search covered the period **2010–2024**, with earlier foundational literature included when mechanistically relevant (e.g., early FGF21 and UCP1 studies).

Search terms were combined using Boolean operators, including:

- *"gene therapy"*, *"AAV"*, *"viral vectors"*, *"RNA interference"*, *"antisense oligonucleotides"*
- *"obesity"*, *"adipose tissue"*, *"thermogenesis"*, *"lipodystrophy"*
- *"FGF21"*, *"UCP1"*, *"leptin–melanocortin"*, *"Hedgehog signaling"*
- *"mesenchymal stem cells"* AND *"gene delivery"*

Reference lists of key articles were screened to identify additional sources. Priority was given to **peer-reviewed original research** and **high-quality reviews** in molecular metabolism, endocrinology, and gene therapy.

Eligibility Criteria

Inclusion criteria

- Studies investigating **gene therapy, gene editing, RNAi, ASO, or vector engineering** for obesity or related metabolic dysfunction.
- Preclinical studies using **mice, rats, or non-human primates**.
- Clinical or translational studies evaluating gene-based modulation of metabolic pathways.
- Review articles providing mechanistic or conceptual frameworks.

Exclusion criteria

- Studies unrelated to obesity or metabolic regulation.
- Papers focusing solely on lifestyle or pharmacologic interventions without genetic components.
- Non-peer-reviewed content unless mechanistically essential (e.g., WHO epidemiology reports).

Data Extraction and Synthesis

Data were extracted manually and cross-verified by thematic grouping. Each study was evaluated for:

- **Type of genetic approach** (AAV, MSC-based delivery, RNAi, ASO, CRISPR).
- **Target gene or metabolic pathway** (FGF21, UCP1, leptin axis, Hedgehog signaling, angiogenesis).
- **Model system** (murine, primate, in vitro, human participants).
- **Therapeutic outcomes** (thermogenesis, insulin sensitivity, adiposity reduction, safety markers).
- **Vector specificity and delivery efficiency**.

A **narrative synthesis** approach was used due to the mechanistic heterogeneity of findings. Results were categorized into major themes:

1. **Adipose-targeted AAV vectors**
2. **FGF21-based gene modulation**
3. **Thermogenic and mitochondrial gene pathways (UCP1, creatine cycling)**
4. **Stem-cell-mediated gene delivery**
5. **RNA interference and antisense platforms**
6. **Emerging precision-medicine and gene-editing strategies**

No meta-analysis was performed because the diversity of study designs (animal models, vector types, delivery routes) precluded quantitative pooling.

Quality Assessment

Given the predominance of preclinical data, study quality was evaluated based on:

- clarity of gene delivery methodology,
- vector characterization and tropism data,
- reproducibility of metabolic outcomes,
- duration of follow-up,
- assessment of safety/immunogenicity.

Clinical studies were assessed using standard indicators of methodological rigor (sample size, control group presence, endpoint definition).

Results

A total of 31 key sources were included in this narrative synthesis, encompassing preclinical mouse and primate studies, vector engineering research, mechanistic metabolic investigations, stem-cell–based delivery platforms, and early-stage clinical RNAi technologies. Findings were organized into thematic domains reflecting major gene therapy strategies for obesity.

1. Adipose-Targeted AAV Gene Delivery

Multiple studies demonstrated that engineered **AAV vectors** can efficiently target adipose depots and induce metabolic improvements [10–12, 16, 26].

Adipose-specific expression of metabolic regulators consistently promoted weight reduction, improved insulin sensitivity, and increased thermogenic activity.

Table 1. Key outcomes of AAV-based preclinical studies

Study	Vector	Target Tissue	Therapeutic Effect	Key Outcomes
Uhrig-Schmidt et al. (2014) [26]	rAAV8	White adipose tissue	Transcriptionally targeted delivery	Improved metabolic profile, efficient adipose transduction
Liu et al. (2014) [12]	Hybrid primate-derived AAV	Adipose tissue	Insulin receptor knockdown	Enhanced insulin signaling and systemic glycemic control
Huang et al. (2024) [6]	Novel adipose-tropic AAV	Adipose; reduced liver tropism	Increased targeting precision	Minimized off-target hepatic expression
O'Neill et al. (2014) [16]	Systemic AAV	Adipose tissue	Adipose-selective transgene expression	Reduced fat mass, metabolic improvement

Overall finding:

Adipose-directed AAV vectors reliably deliver transgenes with high specificity, producing measurable reductions in adiposity and improved metabolic performance.

2. Gene Modulation of FGF21, UCP1, and Thermogenic Pathways

FGF21-based gene delivery demonstrated some of the **most robust anti-obesity effects** across studies.

Similarly, modulation of UCP1, creatine-driven substrate cycling, and Hedgehog pathway inhibition enhanced thermogenesis and contributed to fat mass reduction.

Table 2. Key metabolic regulators and outcomes

Pathway / Gene	Evidence	Metabolic Effect	Representative Studies
FGF21	Strong preclinical efficacy	↓ body weight, ↑ energy expenditure, ↑ insulin sensitivity	Jimenez et al. (2018) [8]; Fisher & Maratos-Flier (2016) [4]
UCP1	UCP1-independent metabolic pathways also relevant	↑ thermogenesis, browning	Samms et al. (2015) [22]; Kazak et al. (2015) [9]
Creatine Cycle	Novel thermogenic mechanism	↑ energy expenditure	Kazak et al. (2015) [9]
Hedgehog inhibition	Promotes beige/brown fat conversion	↑ adipocyte browning	Wang et al. (2019) [27]; Zhang et al. (2020) [30]

Overall finding:

Thermogenic pathway modulation—whether FGF21-driven or UCP1-independent—leads to consistent metabolic improvements and enhanced energy expenditure.

3. Stem-Cell–Based Gene Delivery Approaches

Adipose-derived mesenchymal stem cells (AD-MSCs) exhibit natural homing properties and are emerging as promising vectors for targeted gene delivery.

- Lopez-Yus et al. (2023) [14] showed that AD-MSCs engineered to express metabolic regulators improved systemic glucose tolerance and reduced adiposity in preclinical models.
- AD-MSCs demonstrated **superior targeting specificity**, especially in inflamed or expanding adipose tissue.

Overall finding:

MSC-based delivery offers a complementary, cell-based alternative to viral vectors, with high transduction specificity but requiring further optimization for clinical translation.

4. RNA Interference (RNAi) and ASO-Based Therapeutics

RNAi-based modulation of obesity-driven pathways represents the most clinically advanced approach.

- RNAi inhibition of **ALK7** improved adipose plasticity and reduced fat mass in early translational studies [23].
- INHBE-targeting ASOs showed promising results in suppressing anabolic signaling and reducing adiposity [31].

• These therapies demonstrated favorable safety profiles compared with traditional gene-editing approaches.

Table 3. Summary of RNAi-related findings

Target	Mechanism	Therapeutic Effect	Evidence
7 ALK	RNAi suppression	Reduced adiposity, improved adipocyte function	Sohn (2022) [23]
INHBE	ASO inhibition	Improved metabolic parameters, ↓ adiposity	Zuccaro et al. (2024) [31]

Overall finding:

RNAi/ASO therapies are the most clinically mature gene-based interventions and show strong potential for translation into obesity treatments.

5. Aggregated Findings Across Studies

Therapeutic Benefits Observed Across Gene-Based Strategies

Gene Therapy Mechanisms → Effects → Clinical Relevance
AAV vectors → precise adipose targeting → ↓ adiposity, ↑ metabolic health
FGF21 delivery → ↑ thermogenesis & insulin sensitivity → potential obesity therapy
UCP1/thermogenic modulation → ↑ energy expenditure → fat reduction
MSC-based delivery → targeted adipose transduction → improved metabolic flexibility
RNAi/ASO → pathway-specific suppression → clinically actionable therapies

Consistent outcomes across studies

- **Reduced body weight and fat mass**
- **Improved glucose homeostasis**
- **Enhanced thermogenesis and adipose browning**
- **Sustained metabolic improvements in long-term studies**
- **Increasing precision of vector tropism and safety**

Variability

- Degree of adipose targeting differs among AAV serotypes
- Species-specific metabolic differences
- Long-term safety data remain limited

Narrative Summary of Results

Gene-based interventions consistently demonstrated robust anti-obesity effects across multiple models.

AAV-mediated gene delivery produced sustained expression, leading to significant metabolic improvements. FGF21 gene therapy emerged as one of the most reliable interventions, with multiple independent studies confirming enhanced thermogenesis, improved insulin sensitivity, and substantial fat mass reduction.

Thermogenic gene activation—through pathways such as UCP1, creatine cycling, and Hedgehog inhibition—showed strong potential to increase energy expenditure. RNA interference strategies targeting ALK7 and INHBE provided the first translational bridge into clinical evaluation.

Stem-cell–mediated systems added an additional layer of specificity, reinforcing adipose tissue as a viable therapeutic target.

Together, these findings demonstrate that gene therapy offers substantial mechanistic leverage, directly modifying metabolic pathways rather than relying on symptomatic treatment.

Discussion

The findings of this review demonstrate that gene-based therapeutic strategies offer a promising and increasingly sophisticated approach to addressing the fundamental biological drivers of obesity. Across preclinical models, genetic modulation of adipose tissue and key metabolic pathways consistently produced improvements in energy expenditure, insulin sensitivity, and body composition. These results underscore the potential of gene therapy to intervene upstream in the molecular pathogenesis of obesity, rather than solely mitigating its clinical sequelae.

1. Significance of Adipose-Targeted Gene Delivery

The collective evidence suggests that adipose tissue is not merely a passive energy reservoir but a highly dynamic endocrine organ whose genetic manipulation can yield far-reaching systemic metabolic effects. AAV-based gene delivery has proven especially effective due to its tissue specificity, stable transgene expression, and relatively favorable safety profile. The development of novel adipose-tropic AAV capsids represents an important advance, allowing researchers to overcome historical barriers of off-target hepatic transduction and enabling more precise modulation of adipocyte biology.

Importantly, the metabolic improvements observed following AAV-mediated interventions—including reductions in adiposity, enhanced browning, and increased thermogenesis—support the concept of targeting adipose depots as a strategy to recalibrate whole-body energy balance. These findings align with the growing recognition that the capacity of adipose tissue to store, expend, and distribute energy is central to metabolic health.

2. Pathway-Specific Modulation: Toward Mechanistic Precision

Therapeutic modulation of pathways involving FGF21, UCP1, the leptin–melanocortin axis, and Hedgehog signaling consistently produced marked metabolic benefits. These findings highlight several important implications:

- **FGF21 gene therapy** emerged as one of the most potent interventions, producing durable improvements in thermogenesis and insulin sensitivity across independent models.
- **UCP1-dependent and UCP1-independent thermogenic pathways**, including creatine-driven substrate cycling, expand the landscape of targetable mechanisms for enhancing energy expenditure.
- **Hedgehog signaling inhibition** illustrates how developmental pathways can influence adipose plasticity and browning potential.

Collectively, these results confirm that metabolic flexibility and thermogenic capacity are modifiable traits that can be harnessed therapeutically.

3. Emerging Role of Stem-Cell–Based Delivery Systems

The application of adipose-derived mesenchymal stem cells (AD-MSCs) introduces an innovative cellular platform for gene delivery. Their intrinsic ability to home to inflamed or expanding adipose tissue makes them especially attractive for targeted therapy. While still in early development, MSC-based vectors could ultimately provide an alternative for patients unsuitable for viral vectors or requiring tissue-specific multi-gene modulation.

However, challenges remain regarding scalability, immunogenicity, and regulatory considerations for cell-based products. Further preclinical validation and controlled clinical trials will be necessary to determine their long-term therapeutic viability.

4. Clinical Translation Through RNAi and ASO Technologies

Among the strategies examined, RNA interference (RNAi) and antisense oligonucleotides (ASOs) represent the most immediate translational opportunity. Their mechanism—selective suppression of genes implicated in adipose expansion and anabolic signaling—offers high precision with lower immunogenic risk compared to viral vector–based therapies.

The early success of ALK7 and INHBE-targeted RNAi/ASO platforms suggests that gene-based modulation may soon complement or even surpass conventional obesity pharmacotherapies. These approaches bridge the gap between mechanistic preclinical findings and real-world therapeutic potential.

5. Challenges and Limitations

Despite the promising findings, several limitations and challenges must be acknowledged:

- **Species differences** between rodent and human adipose biology may limit direct translation.
- **Long-term safety data** are scarce, especially concerning immunogenicity, insertional mutagenesis, and sustained gene expression.
- **Vector distribution and tropism** remain areas of active development, with precise adipose targeting still imperfect.
- **Scalability and cost** could pose barriers to clinical implementation, particularly for complex gene therapy platforms.
- **Ethical and regulatory considerations**—including patient selection, reversibility of gene modulation, and equitable access—will shape the path to implementation.

These limitations highlight the need for controlled clinical trials, translational studies in larger animals, and continued refinement of vector engineering.

6. Implications for the Future of Obesity Treatment

The results of this review collectively point toward a paradigm shift in obesity therapeutics:

- From **symptom management** to **molecular intervention**,
- From **short-term weight loss** to **durable metabolic reprogramming**,
- From **non-specific treatments** to **precision medicine** tailored to individual biological profiles.

Gene therapy has the potential to reshape clinical practice, particularly for individuals with severe, treatment-resistant obesity or genetic forms of adipose dysfunction. As advances in CRISPR-based editing, RNAi delivery, and tissue-specific vector engineering continue, the feasibility of safe, reversible, and highly targeted interventions will expand significantly.

Conclusions

The evidence synthesized in this review demonstrates that gene-based therapeutic strategies hold considerable promise for addressing the fundamental biological mechanisms driving obesity. Across preclinical models, targeted genetic modulation of adipose tissue and key metabolic pathways—most notably through FGF21 delivery, thermogenic activation, and suppression of anabolic signaling—consistently produced improvements in energy expenditure, insulin sensitivity, and overall metabolic health. Adipose-tropic AAV vectors and emerging stem-cell–based platforms further highlight the feasibility of achieving tissue-specific gene delivery with increasing precision, while RNA interference and antisense oligonucleotide therapies represent the most clinically advanced candidates to date.

Despite these encouraging findings, significant challenges remain before gene therapy can be broadly implemented in clinical practice. Long-term safety, immune responses, dosing durability, and interspecies differences in adipose biology require continued investigation. Furthermore, ethical, regulatory, and economic considerations will shape the accessibility and real-world impact of these therapies.

Future research should prioritize:

- **Optimization of vector tropism and delivery specificity**, including next-generation AAV capsids and non-viral platforms.
- **Long-term safety and immunogenicity studies** in large-animal and early-phase human trials.
- **Mechanistic mapping of thermogenic and metabolic pathways** to identify new gene targets with high translational potential.
- **Integration of gene therapy with precision-medicine frameworks**, particularly for individuals with monogenic or treatment-resistant obesity.
- **Development of reversible or regulatable gene-modulation systems**, enabling fine-tuned, patient-specific control over metabolic outcomes.

In summary, gene therapy has the potential to redefine obesity treatment by shifting the therapeutic focus from symptomatic management to targeted molecular correction. Continued advancements in gene editing, vector engineering, and metabolic pathway discovery will be essential to unlocking the full therapeutic potential of this rapidly evolving field.

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