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CRISPR-Nanoparticle Delivery Systems for Gene Editing of Obesity and Diabetes Targets

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ABSTRACT

Obesity and type 2 diabetes mellitus (T2DM) are complex polygenic diseases in which environmental factors act on a susceptible genomic background to drive chronic energy imbalance, insulin resistance and β-cell failure. Although current pharmacotherapies improve glycemic control and reduce weight in many patients, they do not correct upstream genetic and epigenetic drivers of disease. CRISPR-based genome editing offers the possibility of durable modification of key metabolic pathways, including brown/beige adipocyte thermogenesis, lipid handling, appetite regulation and pancreatic islet function. However, safe and efficient delivery of CRISPR components to specific metabolic tissues remains a major bottleneck. Nanoparticle platforms like lipid nanoparticles, polymeric carriers, inorganic and hybrid systems are emerging as versatile vehicles for in vivo delivery of CRISPR ribonucleoproteins (RNPs), mRNA and base or prime editors to adipose tissue, liver, skeletal muscle and pancreatic islets. This review discusses the rationale for gene editing in obesity and diabetes, outlines priority genetic targets, and focuses on the design principles and performance of nanoparticle-based CRISPR delivery systems. We highlight preclinical studies that edit genes such as PCSK9, ANGPTL3, Fabp4, Ucp1 regulators and glucoregulatory pathways to improve lipid profiles, insulin sensitivity and body weight in rodent models. Challenges related to tissue specificity, editing efficiency, off-target effects, immunogenicity, manufacturing and ethics are examined, alongside future directions including tissue-tropic nanoparticles, multiplex editing and combinatorial strategies with GLP-1 agonists and lifestyle interventions. By enabling controllable, non-viral delivery of gene editors to metabolic tissues, CRISPR–nanoparticle systems could form the basis of next-generation therapies for obesity-associated diabetes.

Keywords: CRISPR–Cas9; lipid nanoparticles; gene editing; obesity and diabetes; metabolic targets

INTRODUCTION

Obesity and T2DM arise from a confluence of behavioral, environmental and genetic influences, with heritability estimates of 40–70% for body mass index and substantial genetic contributions to insulin secretion and sensitivity[1]. Genome-wide association studies have identified hundreds of loci associated with obesity, T2DM and related traits, many of which converge on pathways regulating adipocyte differentiation, hypothalamic appetite signaling, lipid handling, hepatic gluconeogenesis and β-cell resilience[2–4]. Despite this rich genetic map, most current treatments act downstream of these pathways: lifestyle interventions aim to alter energy balance; pharmacotherapies such as metformin, GLP-1 receptor agonists, SGLT2 inhibitors and insulin analogs modulate glycemia and, to varying degrees, body weight; bariatric surgery restructures the gastrointestinal tract to induce powerful metabolic shifts. None of these, however, directly rewrites the underlying genetic programs that predispose individuals to weight regain, insulin resistance or β-cell exhaustion[5–8].

CRISPR-based genome editing, especially CRISPR–Cas9 and its derivatives (base editors, prime editors, CRISPRa/i), offers a powerful way to modify gene function in a targeted manner. In principle, one could permanently disrupt genes that promote lipogenesis or appetite, activate thermogenic pathways in adipocytes, or correct variants that impair insulin secretion[9–11]. Proof-of-concept studies in mice have shown that CRISPR disruption of Pcsk9 in hepatocytes produces long-lasting reductions in LDL cholesterol, while editing of Angptl3 and other lipid regulators improves triglyceride handling and cardiovascular risk profiles. Similar strategies applied to genes controlling adipose browning, such as negative regulators of UCP1 and PPARγ co-

activators, could increase energy expenditure and counteract obesity[12]. In β-cells, editing of loci that enhance stress resilience or insulin biosynthesis might slow or prevent diabetes progression.
Yet, the central challenge is how to deliver gene editors safely, efficiently and selectively to the relevant tissues in vivo. Viral vectors, particularly adeno-associated virus (AAV), have been widely used for CRISPR delivery, but concerns persist about limited cargo capacity, pre-existing immunity, integration risks, manufacturing complexity and difficulty re-dosing. For chronic, multifactorial conditions like obesity and diabetes where multiple tissues and pathways may require modulation and where re-administration could be necessary, non-viral platforms are attractive. Nanoparticles, especially lipid nanoparticles (LNPs) already validated for mRNA vaccines, have emerged as leading candidates[13, 14].
Nanoparticle-based CRISPR delivery offers several advantages. First, LNPs and related systems can encapsulate Cas9 mRNA plus single guide RNA (sgRNA), or pre-formed Cas9–sgRNA RNP complexes, protecting them from nucleases in circulation and facilitating uptake via endocytosis[13, 15]. LNPs composed of ionizable lipids, helper phospholipids, cholesterol and PEG-lipids can be tuned to optimize endosomal escape, a key determinant of editing efficiency. Second, nanoparticles are transient: once their cargo is delivered, they are cleared, reducing prolonged expression of nucleases and thereby limiting off-target editing. Third, surface modification with targeting ligands or by exploiting endogenous tropism enables preferential delivery to liver, adipose, muscle or islets, moving toward tissue-selective editing. Fourth, nanoparticle formulations are manufactured by scalable microfluidic mixing processes, compatible with industrial production and quality control[13, 16].
For obesity and diabetes, the liver has been a primary focus of CRISPR–LNP research because of its central role in lipid and glucose metabolism and the natural hepatotropism of many LNP formulations. Editing lipid regulators such as PCSK9 or ANGPTL3 may indirectly benefit patients with obesity and T2DM by improving dyslipidemia and cardiovascular risk. However, the specific pathophysiology of diabesity also implicates white and brown adipose depots, skeletal muscle and pancreatic islets[17]. Designing nanoparticles capable of delivering gene editors to these more challenging targets is now an active frontier. Strategies include decorating LNPs with peptides or antibodies recognizing adipocyte or muscle surface markers, or engineering particle size, charge and composition to exploit differential vascular permeability and lymphatic drainage in inflamed or expanding depots[17].
Beyond tissue targeting, the choice of editing modality is critical. Conventional nuclease-active Cas9 introduces double-strand breaks that are repaired by endogenous pathways, enabling gene knockouts but also risking insertions, deletions and chromosomal rearrangements[18]. Base editors, which fuse catalytically impaired Cas9 to deaminase domains, allow precise single-nucleotide conversions without double-strand breaks, suitable for correcting or introducing specific protective variants in monogenic or oligogenic forms of diabetes. Prime editors further expand this toolbox, enabling small insertions and deletions as well as base changes. Delivering these more complex editor constructs increases cargo size demands but may offer superior safety for long-term use in otherwise healthy individuals with obesity or early T2DM[18].
Ethical and practical considerations loom large. Editing in somatic tissues to modify disease risk or progression is conceptually distinct from germline editing, but many of the same concerns about long-term safety, off-target effects and intergenerational perceptions apply. Because obesity and T2DM are influenced by environment and behavior as well as genetics, gene editing cannot be a standalone solution; rather, it must be integrated into a broader framework of lifestyle, pharmacological and societal interventions. Any gene-editing therapy that targets metabolic traits must therefore achieve an attractive risk–benefit balance, with demonstrably low off-target risk and durable, clinically meaningful improvements in metabolic health.
In this context, CRISPR–nanoparticle systems represent a pragmatic compromise: they enable transient, controllable exposure to gene editors, can be adjusted to target specific tissues and genes, and are amenable to iterative refinement[18]. The following sections examine the metabolic gene targets most relevant to obesity and diabetes, the design and performance of nanoparticle platforms for delivering CRISPR payloads, preclinical evidence of efficacy and safety, and the translational hurdles that must be overcome before such therapies can be considered for clinical use in diabesity.

2. Genetic Targets in Obesity and Diabetes Suitable for CRISPR Intervention

Multiple genes along the obesity–diabetes continuum present compelling targets for somatic editing. In the liver, PCSK9 and ANGPTL3 regulate LDL receptor recycling and triglyceride-rich lipoprotein metabolism, respectively; their lifelong loss-of-function in humans confers cardioprotective lipid profiles with relatively few adverse phenotypes, making them attractive for one-and-done editing[19]. Similarly, G6PC and PCK1 modulate gluconeogenesis, and partial modulation of their activity might ameliorate fasting hyperglycemia in T2DM, though with narrower safety margins. In adipose tissue, genes that constrain thermogenesis and browning, such as negative regulators of UCP1, PRDM16 and PGC-1α, are potential candidates for knockdown, as are enzymes involved in de novo lipogenesis[19].
Central regulation of appetite and energy expenditure involves genes such as MC4R, LEPR and POMC, in which rare loss-of-function variants cause severe early-onset obesity. Restoring function through base or prime editing in hypothalamic neurons might, in principle, treat monogenic obesity, but delivery to discrete brain nuclei remains challenging[20]. For more common polygenic obesity, modifying peripheral pathways such as

adipose thermogenesis or gut hormone signalling may be more practical than attempting to reprogram central circuits[20].
In T2DM, β-cell targets include genes involved in insulin processing (PCSK1), glucose sensing (GCK), transcriptional regulation (PDX1, MAFA), unfolded protein response and oxidative stress resistance[21]. Enhancing β-cell resilience through editing protective alleles or silencing pro-apoptotic factors could delay disease progression. For insulin sensitivity, editing of negative regulators of insulin signaling in liver and muscle, such as PTP1B or components of inflammatory cascades, could be envisioned, though systemic effects must be carefully balanced[22, 23].
An appealing strategy is to emulate naturally occurring protective alleles identified in human populations. For example, variants in SLC30A8 (ZnT8) and certain GCK and KCNQ1 haplotypes are associated with reduced T2DM risk or milder disease. Introducing such alleles via precise base editing in at-risk individuals could yield durable protection with minimal disruption to other pathways, provided that editing efficiency and specificity are high in the relevant cell types[24].
Prioritizing targets requires weighing the magnitude of expected metabolic benefit against potential on-target toxicity. Genes whose lifelong inactivation is well tolerated in humans, as evidenced by natural loss-of-function carriers, are especially attractive[24]. Conversely, editing nodes at which modest changes can dramatically shift energy balance, such as key adipose browning regulators, may be powerful but also risk overshooting into cachexia or excessive lipid depletion if not carefully titrated. CRISPR–nanoparticle systems that deliver editors transiently and with adjustable dosing could mitigate some of these concerns by allowing incremental editing rather than global, uncontrolled modification.

3. Design Principles of Nanoparticle CRISPR Delivery Systems for Metabolic Tissues

Nanoparticle platforms for CRISPR delivery in obesity and diabetes must satisfy several design criteria: efficient encapsulation of CRISPR cargo (mRNA, sgRNA, RNP or base/prime editor constructs), protection from degradation, targeted uptake by metabolic tissues, effective endosomal escape, and minimal immunogenicity or off-target accumulation[25]. LNPs have emerged as the leading class due to their track record in mRNA therapeutics. Typical LNP formulations combine an ionizable lipid that is neutral at physiological pH but becomes cationic in endosomes, a helper phospholipid, cholesterol for structural integrity, and a PEG-lipid that controls particle size and circulation. These components self-assemble around nucleic acid cargo via microfluidic mixing, forming ~60–120 nm particles with tunable properties[25].
For liver targeting, relatively simple LNPs rely on apolipoprotein E adsorption and uptake by LDL receptors on hepatocytes, achieving efficient delivery after systemic administration. For adipose and muscle, passive tropism is weaker, necessitating active targeting. Surface conjugation of peptides that recognize adipocyte-specific surface proteins, such as prohibitin or certain integrins, can enhance uptake into white adipose depots[26]. Similarly, ligands for transferrin receptors, VCAM-1 or muscle-specific membrane proteins can bias LNPs toward skeletal muscle vasculature and myofibers. Particle size influences biodistribution: smaller nanoparticles (<80 nm) may penetrate more deeply into tissues, whereas larger ones may remain perivascular[27]. Surface charge also modulates interactions with the glycocalyx and extracellular matrix; slightly negative or near-neutral particles often show better in vivo profiles than strongly cationic ones[27].
Polymeric nanoparticles, such as those based on PLGA, poly(beta-amino esters) or dendrimers, provide alternative scaffolds with distinct release kinetics and mechanical properties. They can encapsulate RNPs or DNA plasmids, though ensuring efficient endosomal escape is more challenging and often requires pH-responsive or membrane-disruptive motifs. Inorganic nanoparticles, including gold, silica and iron oxide, can load CRISPR cargo via surface chemistries and offer imaging capabilities or external field responsiveness, but long-term retention and potential toxicity must be considered carefully, particularly for chronic metabolic indications[28–31]. Hybrid systems that combine lipid shells with inorganic or polymeric cores seek to merge the strengths of each material class.
A key design consideration is the form of CRISPR cargo. Delivering Cas9 mRNA plus sgRNA enables a short pulse of Cas9 expression, after which the mRNA is degraded, limiting the window for off-target editing. Alternatively, encapsulating pre-assembled Cas9 RNPs offers even more transient activity and avoids translation altogether but poses greater formulation challenges due to protein stability and size[32]. Base and prime editors, being larger fusion proteins, may be more readily delivered as mRNA than as RNPs. The choice also interacts with editing goal: for permanent gene knockout in hepatocytes, a single efficient dose may suffice; for partial editing across many adipocytes in a depot, repeated low-dose administration could be preferable[32].
Immunogenicity is another central concern. The Cas9 protein is derived from bacteria, and pre-existing immunity has been documented in humans; repeated exposure could provoke immune responses that neutralize the editor or cause tissue inflammation[33]. LNPs themselves can activate innate immunity via pattern recognition receptors, which was tolerable for vaccines but may be less acceptable in chronic metabolic disease. Strategies to mitigate this include transient immunosuppression, use of orthologous or engineered Cas variants with reduced immunogenic epitopes, and optimization of nanoparticle composition to minimize complement activation and cytokine release[33].
In metabolic tissues already characterized by low-grade inflammation, such as hypertrophic white adipose depots and steatotic liver, the interplay between nanomaterials, immune cells and resident parenchymal cells is

complex. On one hand, leaky vasculature and activated endothelium may facilitate nanoparticle extravasation; on the other, heightened macrophage uptake may divert particles away from target adipocytes or hepatocytes. Therefore, rational design of CRISPR–nanoparticle systems for diabesity must incorporate an understanding of local immunometabolic microenvironments to maximize on-target delivery and minimize off-target sequestration.

4. **Preclinical Applications: Liver Editing and Systemic Metabolic Effects**

The most advanced CRISPR–nanoparticle applications in metabolic disease focus on hepatocytes, given the liver's central role in lipid and glucose homeostasis and its accessibility to LNPs[34]. In mouse models, systemic administration of LNPs carrying Cas9 mRNA and sgRNA targeting Pcsk9 results in efficient knockout of PCSK9 in hepatocytes, durable reduction in circulating PCSK9 protein, increased LDL receptor levels and substantial lowering of LDL cholesterol. Similar approaches targeting Angptl3 or Angptl8 yield favorable shifts in triglyceride and HDL levels[34]. Though these studies primarily aim at cardiovascular risk modification, their relevance to obesity and T2DM lies in the tight linkage between dyslipidemia, ectopic lipid deposition, adipose dysfunction and insulin resistance. Durable correction of atherogenic lipid profiles may mitigate lipotoxic insults to liver and muscle and slow diabesity complications.

Beyond lipid regulators, LNP-mediated editing of genes involved in gluconeogenesis, such as G6pc, has been explored in models of glycogen storage diseases and could inform partial modulation strategies for diabetes[35]. Editing glucose transporters or transcriptional regulators like FoxO1 in hepatocytes might reduce inappropriate hepatic glucose output, improving fasting glycemia[36, 37]. However, such interventions carry higher risk of hypoglycemia and require precise control over editing efficiency, underscoring the advantage of transient, titratable nanoparticle formulations over permanent viral vectors.

Preclinical studies also demonstrate that base editing via LNPs can install protective variants. For instance, cytosine or adenine base editors delivered by LNPs have corrected disease-causing mutations in liver-expressed genes in mouse models, illustrating the feasibility of precise nucleotide changes in vivo. Translating this paradigm to metabolic protection for example, introducing cardio metabolically favorable PCSK9 or ANGPTL3 variants, or T2DM-protective alleles in hepatic regulators could offer long-term benefit from a single or limited number of treatments[35].

Safety assessments in these models are encouraging but not definitive. Off-target editing frequencies have generally been low with optimized guides and transient delivery, and liver function tests often remain normal[38]. Nevertheless, rare events, such as large deletions or chromosomal rearrangements at on-target sites, and unintended edits at sites with partial sequence homology, have been detected, indicating the need for extensive genomic characterization in larger animals and careful human monitoring[38]. In addition, LNP doses required for efficient editing may cause transient elevations in liver enzymes or innate immune activation, suggesting that dosing regimens must be optimized for chronic metabolic indications where risk tolerance is lower than in life-threatening diseases.

5. **Emerging Targets: Adipose Tissue, Skeletal Muscle and Pancreatic Islets**

Extending CRISPR–nanoparticle editing beyond the liver to adipose tissue, skeletal muscle and islets is critical for addressing the core pathophysiology of diabesity. Adipose tissue, particularly visceral white depots, is a major source of inflammatory adipokines and a site of impaired lipid buffering[39]. Editing genes that restrain browning, thermogenesis or adipokine secretion could convert white adipocytes into more metabolically active, insulin-sensitizing cells. Experimental work in mice has shown that nanoparticles decorated with adipose-homing peptides accumulate in subcutaneous and visceral fat and can deliver siRNA or small molecules to modulate gene expression, reducing weight gain and improving insulin sensitivity[39]. Adapting these platforms for CRISPR cargo is a logical next step, though achieving sufficient editing across large adipocyte populations presents a quantitative challenge.

Skeletal muscle is the main site of insulin-stimulated glucose uptake and a source of beneficial myokines[40]. Gene editing could target negative regulators of insulin signaling, enhance oxidative fiber characteristics, or modulate myokines that promote adipose browning and systemic insulin sensitivity. Some studies have used CRISPR–AAV systems to correct muscular dystrophy genes in muscle, illustrating that editing in myofibers is feasible[40]. Translating this to nanoparticle delivery will require particles that efficiently cross muscle endothelium and penetrate myofibers, potentially aided by exercise-induced hyperemia or local physical stimuli such as ultrasound.

Pancreatic islets, particularly β-cells, are appealing but difficult targets due to their dispersed distribution and delicate structure. Nanoparticles that home to islet endothelium or that can be infused via the pancreatic duct might deliver CRISPR editors to β-cells to correct monogenic forms of diabetes or enhance stress resilience[15, 32, 39]. Thus far, most islet-directed gene-editing work remains ex vivo, for example modifying donor islets prior to transplantation. Nonetheless, as nanoparticle targeting strategies improve, in vivo editing of islet genes involved in pro-survival pathways, unfolded protein response modulation or immune evasion could feasibly supplement existing incretin therapies.

In all these tissues, a central translational question is how much editing is needed to achieve clinically meaningful effects. Unlike monogenic liver diseases where correcting a fraction of hepatocytes may suffice, obesity and T2DM involve subtle shifts across large tissue masses[21, 41]. Partial editing of a few percent of adipocytes or

myofibers may modestly affect local metabolic tone but might not translate into large systemic changes. Conversely, editing stem/progenitor cells or niche regulators that orchestrate tissue remodeling could have outsized impacts from relatively small editing fractions. Understanding these quantitative relationships will guide dosing strategies and inform whether CRISPR–nanoparticle approaches should be positioned as stand-alone interventions or as adjuncts to GLP-1 agonists, SGLT2 inhibitors and lifestyle programs.

6. **Safety, Manufacturing and Ethical Considerations in Diabesity Gene Editing**

Applying CRISPR–nanoparticle systems to common metabolic diseases raises a distinct safety and ethical landscape compared with treating rare, life-threatening disorders. Individuals with obesity and T2DM vary widely in disease severity and comorbidities, and many respond well to existing therapies[42]. The tolerance for risk from irreversible gene edits is therefore lower, emphasizing the need for exceptional specificity, minimal off-target effects and robust long-term safety data. Nanoparticle delivery reduces but does not eliminate risks related to innate immune activation, complement activation and potential accumulation in off-target organs such as spleen and lymph nodes[42].

Manufacturing considerations are substantial. LNPs and related nanoparticles must be produced under strict quality control, with tight control over particle size, composition, encapsulation efficiency and stability[43]. Scaling microfluidic production while maintaining batch consistency is challenging but feasible, as demonstrated by mRNA vaccine manufacturing. For CRISPR cargo, sgRNA and mRNA synthesis must ensure high purity and minimal immunostimulatory contaminants. For base or prime editors, larger coding sequences increase the demands on formulation and may reduce encapsulation efficiency, requiring further optimization[43].

Ethically, gene editing for metabolic indications touches on concerns about medicalization of lifestyle, equity of access and potential stigmatization. If high-cost gene editing therapies are available only to a small subset of patients in high-income settings, global disparities in obesity and diabetes burden could widen[44]. There is also the risk that focus on genetic solutions diverts attention from environmental and social determinants of diabesity, such as food environments, socioeconomic disadvantage and physical inactivity. To mitigate these risks, CRISPR–nanoparticle interventions should be framed as complementary to, not replacements for, population-level prevention and behavior-oriented therapies. Fair allocation, affordability and inclusion of diverse populations in clinical trials will be crucial[44].

Regulatory frameworks will likely treat CRISPR–nanoparticle therapies for diabesity as advanced medicinal products, requiring extensive preclinical toxicology, biodistribution and off-target analyses, followed by carefully staged clinical trials with long-term follow-up. Given that metabolic improvements may unfold over months to years, while editing occurs acutely, robust post-marketing surveillance systems will be needed to detect late adverse events, including malignancy risk or unexpected metabolic perturbations.

7. **Future Directions: Toward Programmable, Tissue-Specific Metabolic Gene Editing**

Looking forward, several trends are likely to shape the evolution of CRISPR–nanoparticle therapies for obesity and diabetes. One is increasing tissue specificity through "tropism-by-design" nanoparticles that combine optimized size, charge and composition with ligands for receptors enriched on adipocytes, hepatocytes, myofibers or β-cells. Such systems could reduce total dose requirements and limit off-target exposure, improving safety and cost-effectiveness[45]. Another trend is multiplex editing: delivering multiple sgRNAs with a single nanoparticle dose to simultaneously modulate several nodes in a metabolic pathway, for example knocking down a lipogenesis enzyme while activating a thermogenic regulator, or editing both lipid and glucose regulators in the liver[45].

Advances in editor technology will also matter. More precise base and prime editors with smaller footprints and reduced off-target activity will make it safer to install protective alleles without double-strand breaks. RNA-targeting CRISPR systems (Cas13 and related) could offer reversible modulation of metabolic transcripts without permanent DNA edits, an appealing option for early-stage diabesity or in populations wary of irreversible gene changes[46]. Integration with synthetic biology circuits where gene-editing activity is gated by metabolic cues, small molecules or light could enable context-dependent editing, further refining safety.

Combining CRISPR–nanoparticle therapies with existing metabolic drugs and lifestyle interventions may yield synergistic benefits. For instance, editing adipose or hepatic pathways that potentiate weight loss or glycemic responses could enhance the durability and magnitude of GLP-1 receptor agonist effects, potentially allowing dose reduction and fewer side effects[46]. Exercise programs might be paired with muscle-targeted editing that amplifies myokine responses, reinforcing benefits on adipose browning and insulin sensitivity. Such combinatorial strategies highlight the need to view gene editing as one tool among many in a holistic metabolic care paradigm.

CONCLUSION

CRISPR–nanoparticle delivery systems represent a promising frontier for durable, tissue-directed intervention in obesity and diabetes, conditions traditionally managed through lifestyle modification and chronic pharmacotherapy. By enabling transient, programmable delivery of powerful gene-editing tools to the liver, adipose tissue, skeletal muscle and pancreatic islets, these platforms could rewire key metabolic pathways, emulate protective human variants and enhance energy expenditure and insulin sensitivity. Preclinical studies, particularly in hepatocytes, already demonstrate robust editing and favorable metabolic shifts, while emerging work in adipose and muscle points to broader potential. Significant challenges remain in achieving precise tissue

targeting, minimizing off-target and immune effects, scaling manufacturing and navigating ethical and regulatory landscapes, particularly for common, multifactorial diseases. Future progress will depend on continued innovation in nanoparticle chemistry and editor design, rigorous safety assessment and thoughtful integration with established therapies and public health measures. If these hurdles can be overcome, CRISPR–nanoparticle systems may become an important component of next-generation, precision approaches to preventing and treating obesity-associated diabetes.

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