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## Lipid-Based Nanocarriers for Modulating Adipogenesis and Lipid Metabolism: Emerging Anti-Obesity Strategies

Bwambale Isaac

Biomedical Department Kampala International University Uganda

Email: isaac.bwambale@studwc.kiu.ac.ug

### ABSTRACT

Obesity is characterized by chronic energy surplus, hypertrophic and hyperplastic expansion of white adipose tissue, ectopic lipid deposition and complex disturbances in lipid and glucose metabolism. Pharmacologic approaches that directly modulate adipogenesis, lipogenesis, lipolysis and fatty acid oxidation have often been limited by poor solubility, low oral bioavailability and off-target effects of many candidate compounds, including natural products and nucleic-acid-based agents. Lipid-based nanocarriers such as liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions and lipid nanoparticles provide a versatile platform to overcome these limitations by enhancing solubility, protecting labile cargos and improving delivery to adipose tissue and metabolic organs. This review highlights the pathophysiological rationale for targeting adipogenesis and lipid metabolism in obesity and explains how lipid-based nanocarriers can be engineered to modulate these processes. We describe major nanocarrier classes and design features, discuss mechanisms through which they influence adipocyte differentiation and lipid handling, and summarize preclinical evidence for lipid-based delivery of small molecules, nutraceuticals, endogenous lipids and nucleic acids. Finally, we address safety, scalability, regulatory issues and future directions toward precision, adipose-targeted nano-therapies for obesity.

**Keywords:** Obesity; Adipogenesis; Lipid metabolism; Lipid-based nanocarriers; Nanomedicine

### INTRODUCTION

Obesity reflects a long-standing imbalance between energy intake and expenditure, but at the cellular level, it is fundamentally a disease of dysregulated adipose tissue remodeling and lipid metabolism [1-4]. In response to chronic caloric excess, white adipose tissue expands through a combination of adipocyte hypertrophy and recruitment of new adipocytes from mesenchymal stem and preadipocyte pools. This process, termed adipogenesis, is orchestrated by a transcriptional cascade involving C/EBP $\beta$  and C/EBP $\delta$ , followed by the master regulators PPAR $\gamma$  and C/EBP $\alpha$ , which drive the expression of genes required for lipid uptake, storage, and endocrine function. Parallel pathways, including SREBP1c and ChREBP, control de novo lipogenesis, while enzymes such as hormone-sensitive lipase and adipose triglyceride lipase regulate lipolysis [5-9].

In early stages, controlled adipogenesis allows safe sequestration of surplus lipids in subcutaneous depots. Over time, however, excessive hypertrophy and limited adipogenic capacity lead to adipose dysfunction. Adipocytes become hypoxic, pro-inflammatory and insulin resistant, secrete altered profiles of adipokines and cytokines and release excess free fatty acids [6, 10, 11]. Surplus lipids spill into the liver, skeletal muscle and pancreas, causing ectopic steatosis, lipotoxicity and systemic insulin resistance. The resulting metabolic syndrome greatly increases the risk of type 2 diabetes, non-alcoholic fatty liver disease and cardiovascular disease.

Therapeutic strategies targeting adipogenesis and lipid metabolism seek either to restrain adipocyte differentiation and lipid storage, to promote healthy remodeling with enhanced lipid oxidation and thermogenesis or to redirect lipids away from harmful ectopic sites [6, 8, 12]. In vitro and in vivo studies show that a wide range of small molecules, including PPAR modulators, AMPK activators, phytochemicals and specific fatty acids, can inhibit adipogenesis, reduce lipogenesis or enhance fatty acid oxidation. Gene-based interventions, such as miRNAs that repress pro-adipogenic transcription factors, provide further means to modulate these pathways [13, 14].

Yet translation of these findings into clinically meaningful anti-obesity therapies has proved difficult. Many promising compounds are hydrophobic, chemically unstable or extensively metabolized, resulting in poor oral bioavailability and low exposure at adipose and hepatic targets [15]. Others require high systemic doses to

achieve effective concentrations in adipose tissue, increasing the risk of off-target effects in cardiovascular, hepatic or central nervous systems. Nucleic acid cargos such as miRNAs and siRNAs are rapidly degraded in circulation and poorly taken up by adipocytes without a delivery vehicle[15].

Lipid-based nanocarriers offer a coherent strategy to overcome these obstacles. Compared with polymeric or inorganic nanoparticles, lipid-based systems generally display superior biocompatibility and biodegradability, as they are constructed from physiological or food-grade lipids that can be metabolized through normal pathways.[16–18]. Major classes include liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanoemulsions and more recently ionizable lipid nanoparticles and lipid–polymer hybrids. These platforms can solubilize hydrophobic drugs within lipid matrices, protect them from gastrointestinal and enzymatic degradation, control their release profile and alter biodistribution through modulation of particle size, surface charge and surface ligands[15].

For obesity in particular, lipid-based nanocarriers provide three critical advantages. First, they can dramatically improve the bioavailability of lipophilic anti-obesity molecules such as curcumin, resveratrol, conjugated linoleic acid, hesperidin and other nutraceuticals, which have strong anti-adipogenic and lipid-modulating activity in vitro but limited clinical efficacy in conventional formulations[19]. Second, they can be engineered to preferentially accumulate in adipose tissue or liver, either passively through size and surface property tuning or actively via ligands that recognize adipocyte or hepatic receptors, thereby increasing on-target concentrations while reducing systemic exposure. Third, they provide a compatible environment for lipidic or nucleic acid cargos that directly modulate adipocyte differentiation, such as anti-adipogenic miRNAs or endogenous lipid mediators, effectively turning the carrier itself into part of the therapeutic strategy[19].

Recent reviews explicitly highlight lipid-based nano-carriers as an emerging platform for delivery of anti-obesity natural compounds and other agents, emphasizing their ability to improve solubility, stability and targeted delivery while enabling controlled release and adipose-focused action. In parallel, conceptual frameworks for adipose tissue-targeting nanomedicines place lipid-based systems alongside polymeric and biomimetic carriers as key tools for future obesity pharmacotherapy.

Against this backdrop, it is increasingly plausible to design nanoformulations that specifically modulate adipogenesis and lipid metabolism in white and brown adipose tissue and liver, rather than relying on systemic exposures that indiscriminately affect multiple organs. The remainder of this review outlines the main lipid-based nanocarrier platforms, explains how they can be tuned to affect adipocyte biology and lipid pathways, and examines the growing preclinical evidence supporting their use in obesity models.

## **2. Classes and Design Principles of Lipid-Based Nanocarriers**

Lipid-based nanocarriers encompass a family of colloidal systems whose structures mimic or build upon natural lipid assemblies. Liposomes are among the earliest and best-characterized examples, consisting of phospholipid bilayers surrounding an aqueous core. Hydrophilic drugs can be loaded into the core, whereas lipophilic molecules partition into the bilayer. Surface modification with polyethylene glycol improves circulation time, and attachment of targeting ligands such as peptides or antibodies confers tissue selectivity[20–22].

Solid lipid nanoparticles, introduced in the early 1990s, employ a matrix of solid lipids that remain solid at body temperature, typically stabilized by surfactants in aqueous dispersion. Particle sizes usually range from 50 to 500 nm. SLNs combine the advantages of traditional emulsions and polymeric nanoparticles, offering protection of labile compounds, controlled release, and compatibility with large-scale manufacturing, although drug expulsion during storage and limited loading capacity can be concerns[23, 24]. Nanostructured lipid carriers were developed as a second-generation improvement over SLNs. They incorporate a blend of solid and liquid lipids, generating a less ordered internal matrix with more imperfections that can accommodate higher drug loads and reduce expulsion upon crystallization[25]. NLCs also allow finer tuning of release kinetics and have shown enhanced stability relative to SLNs.

Nanoemulsions, typically oil-in-water systems with droplet sizes in the 20–200 nm range, use surfactants and sometimes co-surfactants to stabilize dispersed lipid phases[26]. They are thermodynamically or kinetically stable, transparent or translucent, and well-suited to solubilize highly hydrophobic compounds. Food-grade nanoemulsions for oral delivery of nutraceuticals such as curcumin and carotenoids have received particular attention in obesity-related applications[26]. More recently, ionizable lipid nanoparticles, popularized by mRNA vaccines, and lipid–polymer hybrid nanoparticles have expanded the toolbox. These systems excel at encapsulating nucleic acids and other charged cargos while retaining lipid-associated advantages in biocompatibility and endosomal escape. Biomimetic variants, such as exosome-mimetic vesicles or lipoprotein-inspired particles, add another layer of sophistication and may exploit natural lipid transport pathways[26].

Across all classes, key design parameters include particle size and polydispersity, surface charge, lipid composition, drug loading and release characteristics. These properties determine not only pharmacokinetics and biodistribution, but also interactions with adipocytes, macrophages and liver cells[27]. For obesity applications, design tends to favor nanometer-scale sizes that avoid rapid renal clearance but can access the fenestrated vasculature of adipose tissue and liver, neutral or slightly negative surface charge to reduce opsonization and carefully chosen lipids that maintain stability while supporting controlled release of the anti-obesity cargo.

### 3. Mechanisms for Modulating Adipogenesis and Lipid Metabolism with Lipid Nanocarriers

Lipid-based nanocarriers modulate adipogenesis and lipid metabolism both by improving the delivery of active molecules and through their own lipid components[28]. In most designs, the primary effect stems from the encapsulated cargo. Anti-adipogenic small molecules, including plant-derived polyphenols and synthetic PPAR or AMPK modulators, show markedly greater activity in 3T3-L1 and primary adipocyte models when delivered via SLNs, NLCs or liposomes compared with free drug, reflecting higher cellular uptake and sustained intracellular exposure[28].

For example, conjugated linoleic acid and  $\alpha$ -tocopherol, both capable of inhibiting adipogenesis, display enhanced anti-adipogenic effects in vitro and in high-fat diet rat models when co-delivered in tocol-based NLCs[29]. Curcumin and resveratrol nanoformulations similarly downregulate PPAR $\gamma$  and C/EBP $\alpha$  expression, reduce lipid accumulation and increase expression of fatty acid oxidation genes at lower doses than their free counterparts[30–32].

Nucleic acid cargos add a mechanistically distinct layer. Anti-adipogenic miRNAs delivered in lipid nanoparticles can directly repress mRNAs encoding pro-adipogenic factors, thereby interfering with the differentiation cascade[33]. A recent study described lipid nanoparticles as shuttles for anti-adipogenic miRNAs into human adipocytes, highlighting their potential to modulate adipogenesis at the post-transcriptional level. Similar approaches could be used for siRNAs targeting SREBP1c, ACC or other lipogenic enzymes[33]. Carrier lipids themselves may influence adipocyte biology. Endogenous lipids such as omega-3 fatty acids or specialized pro-resolving mediators included in nanocarrier formulations can contribute to anti-inflammatory and lipid-modulating effects[34]. One experimental study co-formulated a herbal anti-obesity active with endogenous lipid mediators into lipid nanocarriers and observed synergistic improvements in weight, cholesterol and adipose inflammation compared with either component alone, suggesting that rational selection of carrier lipids can amplify therapeutic outcomes[34].

Lipid-based nanocarriers may also preferentially interact with adipocytes and adipose-resident macrophages through mechanisms such as lipoprotein lipase-mediated uptake, scavenger receptor recognition or fusion with plasma membranes[35]. These interactions enhance intracellular delivery of encapsulated drugs and can modulate local inflammatory states that affect adipogenesis and lipolysis. At the tissue level, improved delivery of agents that promote browning or thermogenesis, such as certain polyphenols or PPAR $\delta$  agonists, could shift white adipose tissue toward a more oxidative, energy-dissipating phenotype, indirectly affecting lipid metabolism[35].

Altogether, lipid-based nanocarriers function not merely as passive delivery vehicles but as integrated systems in which cargo and carrier lipids jointly influence adipocyte differentiation, lipid storage and oxidative pathways, providing multiple levers for anti-obesity intervention.

### 4. Adipose Tissue–Targeting Lipid Nanocarriers

Achieving preferential accumulation of anti-obesity cargos in adipose tissue is a key step toward maximizing efficacy while minimizing off-target effects. Recent reviews on adipose tissue–targeting nanomedicines highlight lipid-based systems as particularly promising due to their ability to encapsulate lipophilic drugs and mimic endogenous lipoproteins.

Passive targeting leverages structural and physiological features of adipose tissue. Obese adipose depots often display increased vascular permeability and altered extracellular matrix composition, which can favor nanoparticle extravasation and retention[36]. Nanocarriers with sizes in the 50–200 nm range and appropriately tuned surface properties may accumulate more readily in such depots, akin to the enhanced permeability and retention effect observed in tumors, although this remains less well characterized in adipose tissue[36].

Active targeting adds specificity by decorating nanocarrier surfaces with ligands that recognize adipocyte or adipose vasculature markers. Peptides that bind prohibitin, integrins or other proteins enriched on adipose endothelium have been used to direct nanoparticles to fat depots in vivo, significantly increasing local drug concentrations[37]. In principle, liposomes, SLNs or NLCs loaded with anti-adipogenic agents or browning promoters and functionalized with such ligands could selectively modulate white and brown adipose tissue[37]. Some formulations exploit endogenous lipid transport pathways. Lipid nanoemulsions and lipoprotein-mimetic particles can be processed by lipoprotein lipase, leading to uptake of remnant particles and associated drugs by adipocytes and macrophages via receptors such as LDL receptor–related proteins and scavenger receptors. Tailoring the lipid composition and apolipoprotein content of nanocarriers may thus bias their distribution toward adipose tissue[30].

In an illustrative preclinical study, conjugated linoleic acid and  $\alpha$ -tocopherol loaded into tocol-based NLCs showed improved delivery to liver and adipose tissue and stronger inhibition of adipogenesis compared with free compounds[38]. Similar strategies using hesperidin-loaded NLCs in microneedle patches or resveratrol-loaded NLCs embedded in dissolving microneedles have been explored for transdermal targeting of subcutaneous adipose tissue, with promising anti-obesity effects in animal models[38].

Collectively, these approaches suggest that adipose tissue–targeted lipid nanocarriers can concentrate anti-obesity agents where they are most needed, reduce systemic exposure and potentially allow new combinations of drugs that would be too toxic at systemic levels. Detailed mapping of depot-specific vascular and molecular

signatures, along with careful choice of lipid compositions and targeting ligands, will be essential to convert these concepts into clinically meaningful therapies.

### **5. Lipid-Based Delivery of Nutraceuticals, Endogenous Lipids and Combination Therapies**

Many nutraceuticals and plant-derived compounds with anti-adipogenic and lipid-lowering activity suffer from poor aqueous solubility and low bioavailability[39]. Lipid-based nanocarriers have therefore been widely applied to such agents as part of anti-obesity strategies. Recent work highlights that nanoemulsions, SLNs, NLCs and phytosome-type lipid complexes can markedly improve stability, intestinal absorption and systemic exposure of curcumin, resveratrol, green tea catechins, hesperidin and other phytochemicals[39].

For example, curcumin-loaded SLNs and NLCs not only enhance chemical stability and intestinal absorption but also exert stronger effects on body weight, adiposity and lipid profiles in high-fat diet animal models than equivalent doses of free curcumin. Hesperidin encapsulated in hyaluronic acid-based NLCs and incorporated into microneedles has shown improved anti-obesity efficacy compared with conventional formulations, illustrating how nanocarriers and alternative administration routes can be combined[40]. Endogenous lipids incorporated into nanocarriers can also be therapeutic. Co-delivery of herbal actives with specific lipid mediators in lipid nanocarriers has yielded greater reductions in body weight, adiposity and serum lipids than either component alone, suggesting that synergistic interactions between the active and carrier lipids can be harnessed. Conjugated linoleic acid, omega-3 fatty acids and  $\alpha$ -tocopherol are examples of lipids with intrinsic anti-adipogenic or lipid-modulating properties that have been formulated within lipid nanocarriers to potentiate their effects[41].

Combination nanoformulations extend this concept further. Multi-drug lipid nanocarriers can co-encapsulate agents with complementary mechanisms, such as a phytochemical AMPK activator and a PPAR modulator, or a nutraceutical with an approved anti-obesity drug, providing controlled, synchronized delivery to adipose tissue or liver[41]. In principle, such systems could lower the required dose of synthetic agents, reducing side effects while exploiting the multi-target actions of nutraceuticals. From a formulation standpoint, the food-compatible nature of many lipid excipients facilitates development of functional foods and nutraceutical beverages containing nanoemulsified anti-obesity agents, potentially offering preventive strategies for at-risk populations[42]. However, the line between food and drug becomes blurred in these cases, raising regulatory and labeling questions that must be addressed carefully.

### **6. Safety, Scalability and Regulatory Considerations**

For lipid-based nanocarriers to play a meaningful role in obesity therapy, they must demonstrate favorable safety profiles, scalable manufacturing and clear regulatory pathways. Lipid-based systems enjoy inherent advantages because many component lipids and surfactants are endogenous or generally recognized as safe[43]. SLNs and NLCs have been extensively studied in pharmaceutical and cosmetic contexts and are generally regarded as biocompatible and non-toxic when appropriately formulated. Nevertheless, chronic administration in obesity, often over years, requires rigorous evaluation[43].

Key safety concerns include potential accumulation of non-metabolizable lipids, surfactants or stabilizers in the liver, spleen or reticuloendothelial system; induction of oxidative stress or inflammation; and unexpected effects of nanoscale properties on biodistribution and cellular interactions[44]. In vitro studies on 3T3 fibroblasts and other cell lines indicate that SLNs and NLCs can be well tolerated, but some formulations may impair viability or trigger stress responses depending on composition and dose. Translating these data into safe human dosing regimens will require careful toxicology across species[44].

Manufacturing at scale presents practical challenges. Although high-pressure homogenization, microfluidization and solvent diffusion techniques for SLNs and NLCs are well established and industrially scalable, maintaining tight control over particle size, polydispersity, encapsulation efficiency and stability across large batches is non-trivial. Lyophilization or spray drying may be necessary to improve shelf life, adding cost and complexity[45]. For nutraceutical applications, cost constraints are particularly stringent, as formulations must remain affordable for long-term use in broad populations.

Regulatory classification depends on intended use and claims. Nanoformulated phytochemicals or endogenous lipids intended for treatment or prevention of obesity and related diseases will typically be regulated as medicinal products, requiring demonstration of quality, safety and efficacy through phased clinical trials[46]. If positioned as functional foods or dietary supplements, regulatory requirements may be less stringent but still evolving, especially where nanotechnology is involved. Transparent labeling and evidence-based claims are essential to avoid eroding trust[46].

Equity and access are broader considerations. Advanced nanomedicines risk being confined to high-resource settings and affluent patients. Yet obesity prevalence and its metabolic complications are rising fastest in low- and middle-income countries[47]. Designing lipid-based nanocarriers with inexpensive, widely available excipients and robust, room-temperature-stable formulations could help bridge this gap, but intentional effort will be needed to ensure that nano-enabled anti-obesity strategies do not exacerbate existing health disparities.

### **7. Future Directions: Toward Precision, Adipose-Targeted Nano-Therapy**

Looking ahead, lipid-based nanocarriers are likely to become increasingly sophisticated and integrated into precision medicine frameworks for obesity. As single-cell and spatial omics reveal finer-grained maps of adipose tissue heterogeneity, including distinct subpopulations of adipocytes, progenitors, macrophages and endothelial

cells, new molecular targets for nanocarrier ligands will emerge[48]. Lipid nanoparticles decorated with ligands that recognize, for example, pro-inflammatory adipose macrophages or beige adipocyte precursors could deliver cargos that selectively reprogram these cell populations[48]. Integration with genomic, metabolomic and microbiome profiling will support patient stratification. Individuals whose obesity is dominated by visceral adipose expansion and hepatic steatosis might benefit most from liver- and visceral fat-targeted lipid nanocarriers loaded with lipogenesis inhibitors or fatty acid oxidation boosters. Others with strong inflammatory signatures could receive formulations enriched in anti-inflammatory nutraceuticals and endogenous lipids[49].

Lipid-based nanocarriers will also increasingly carry complex cargos. Anti-adipogenic miRNAs, siRNAs targeting lipogenic enzymes and CRISPR-based tools for reversible gene modulation could be encapsulated alongside small molecules or nutraceuticals to achieve multi-level control of adipogenesis and lipid metabolism[49]. Theranostic designs in which nanocarriers include imaging agents or responsive probes could allow clinicians to monitor depot-specific accumulation and perhaps metabolic responses in vivo, informing dose titration and patient selection[49, 50].

Combination regimens are another frontier. Lipid nanocarriers may be used to co-deliver phytochemicals or endogenous lipids with low-dose GLP-1 receptor agonists, SGLT2 inhibitors or other approved drugs, potentially enhancing efficacy while reducing systemic exposure to synthetic agents. Conversely, successful lifestyle interventions might be supported by nanoformulated nutraceuticals that stabilize beneficial adipose and hepatic remodeling, lowering relapse risk.

Realizing these possibilities will require continued progress in understanding nano-bio interactions in adipose tissue and liver, refining targeting ligands, improving manufacturing robustness and generating high-quality clinical trials that move beyond surrogate endpoints to hard outcomes such as sustained weight loss and reduction in diabetes incidence. Regulatory frameworks must adapt to evaluate increasingly complex nanoformulations that blur boundaries between drug, device and biologic.

If these challenges can be addressed, lipid-based nanocarriers have the potential to shift obesity treatment from broad systemic pharmacology toward depot- and pathway-specific modulation of adipogenesis and lipid metabolism, embedded in a broader ecosystem of lifestyle, environmental and policy interventions.

#### CONCLUSION

Lipid-based nanocarriers have emerged as versatile tools for modulating adipogenesis and lipid metabolism, addressing key limitations of traditional anti-obesity agents. By enhancing solubility, stability and bioavailability of hydrophobic drugs and nutraceuticals, and by enabling targeted delivery to adipose tissue and liver, liposomes, solid lipid nanoparticles, nanostructured lipid carriers and related systems can amplify anti-adipogenic, lipolytic and lipid-oxidizing effects at lower doses. Preclinical studies with phytochemicals, endogenous lipids and nucleic acids provide compelling proof-of-concept that nanoformulation improves metabolic outcomes, and adipose-targeted designs promise further gains in efficacy and safety. Important hurdles remain in terms of long-term safety, scalable manufacturing, regulatory classification and equitable access. Nonetheless, as nanotechnology converges with advances in adipose biology and precision medicine, lipid-based nanocarriers are well positioned to contribute to next-generation, mechanism-based anti-obesity strategies that move beyond one-size-fits-all pharmacotherapy toward more targeted and sustainable control of energy storage and lipid homeostasis.

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