RESEARCH PAPER

# Emerging Biomaterial, Non-Surgical and Minimal Invasive Therapies Based Strategies for the Management of Hyperlipidemia

**Dr. Vikas R. Dhole [1], Miss. Sakshi D. Sawant[1*], Dr Sanganna C. Burli[1], Dr. Prashant S. Kumbhar[1], Ms. Ashwini M. Mane[1]**

*[1]Department of Pharmacology, Ashokrao Mane College of Pharmacy, Peth-Vadgaon, Kolhapur, Maharashtra, India.*

** Corresponding Author: Ms. Sakshi D. Sawant, Department of Pharmacology, Ashokrao Mane College of Pharmacy, Peth-Vadgaon, Kolhapur, Maharashtra, India. Email: sakshisawant519@gmail.com*

**ABSTRACT**

Hyperlipidemia remains one of the major contributing risk factors for cardiovascular diseases. Current therapies for its treatment have significant drawbacks regarding their pharmacokinetic profile and adverse effects. This review presents recent progress in biomaterials-based nanocarriers that have been designed to enhance targeted delivery into hepatocytes and adipocytes. Such pathways can be involved through the LDL receptor, scavenger receptor, and PPAR signaling by the nanocarriers to increase cholesterol clearance, stimulate lipolysis, and reduce hepatic steatosis. In addition to these targeted approaches, the review covers minimally invasive therapies. Those include intragastric balloons, endoscopic sleeve gastrostomy, aspiration therapy, and injections of glucagon-like peptide-1 receptor agonists into the stomach. The latter group of interventions promotes satiety and induces changes in gut hormones, notably increasing GLP-1 and related peptide expression. The resulting hormonal shifts stimulate fat oxidation and contribute to improved and more durable lipid profiles. Together, these approaches constitute multi targeting, patient-centered opportunities that bring us closer to managing hyperlipidemia in a personalized way.

**Keywords:** Hyperlipidemia, nano-carriers, biomaterial, invasive therapy, fat oxidation, multitargeting, gut hormones, receptors.

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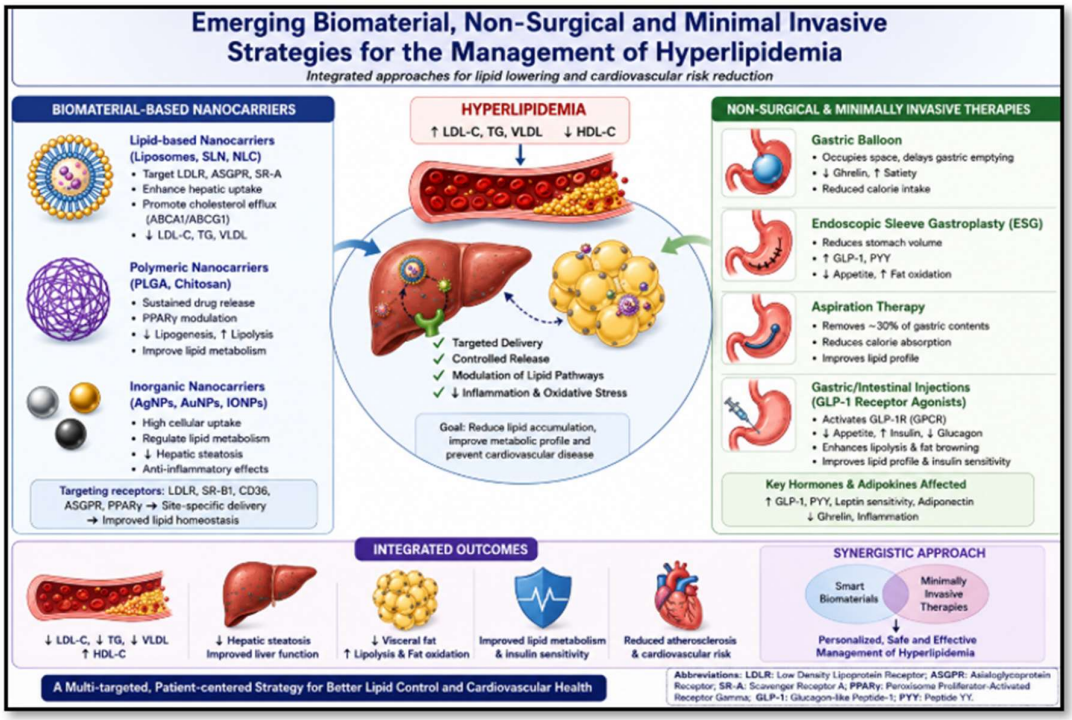



**Graphical Abstract**

## INTRODUCTION

Hyperlipidemia is defined as a chronic metabolic disorder resulting in persistently high plasma levels of cholesterol, triglycerides, low-density lipoproteins (LDL), and very-low-density lipoproteins (VLDL), accompanied in most cases by lower-than-desirable levels of high-density lipoproteins (HDL), known as lipoproteins that have intense cardio-protective properties [1]. At a cellular and molecular level, it results in an overabundance of lipid cell uptake and storage in cells such as hepatocytes, lymphocytes, macrophages, and smooth muscle cells of blood vessels, resulting in uneven or aberrant fatty matter deposition in cells and tissues. Retention of LDL in the intimal layer of arterial walls is believed to be one of first pathological changes that occur in hyperlipidemia-induced cardiovascular diseases [2]. On prolonged periods of disturbed lipid profiles in blood plasma, retention of lipids in arterial walls propagated by macrophages culminates in the production of foam cells that eventually give rise to white spots of fatty plaques in arterial walls resulting in gradual development of lipids in arterial walls [3], contributing massively to cardio-vascular diseases and deaths that are increasingly becoming global phenomena in healthcare standards [3]. Presently, there has been a dramatic shift in the treatment approaches for hyperlipidemic from lifestyle changes to pharmacotherapy using statins, fibrates, bile acid sequestrants, cholesterol absorption inhibitors, and most recently, PCSK9 inhibitors [4]. Although immense progress has been made in lowering cardiovascular risk, adherence issues, side effects, interindividual variability in pharmacodynamics, and persistent risk due to optimal lipid treatment have generally limited its long-term efficacy [5]. Moreover, conventional systemic drug delivery systems lack tissue-specificity with frequent recourse to non-target organs, thereby promoting higher chances of systemic toxicity. These limitations create a tremendous demand for new approaches with greater potential for efficient delivery, prolonged efficacy, and less invasive procedures. Developments in biomaterials research have provided tremendous potential in understanding the multifaceted pathophysiology associated with hyperlipidemia. Biomaterial-based nanoparticles like lipid nanoparticles, polymer-based nanocarriers, inorganic nanoparticles, and biomimetic models have presented tremendous opportunity for drug delivery to lipid-laden cellular sites and atherosclerotic plaques [6, 7]. By improving drug stability and promoting uptake through a receptor-mediated mechanism, these systems have promise in improving lipid-lowering effectiveness while reducing systemic drug exposure. However, intelligent biomaterials sensitive to local physiological cues, such as pH, oxidative stress, and enzymatic activity, are being developed for site-specific therapy in the lipid-laden and inflamed vascular territories [8]. Alongside advances in biomaterials, non-surgical and minimally invasive therapies are being considered as efficacious modalities for lipid and fatty tissue reduction. These modalities include endoscopic procedures, intragastric balloons, and aspiration therapy, as well as local injectable systems, for lipid absorption inhibition and modulation of appetite hormones, in an effort to avoid major surgery-related complications [9]. These methods, when integrated with biomaterials-based delivery systems, present a promising avenue for long-term control of lipids with enhanced patient compliance and faster recovery times. These treatment modalities can benefit patients who do not qualify for surgery or who cannot tolerate pharmacotherapy for a prolonged period Due to the escalating prevalence of hyperlipidemia and its complications, there is a pressing need for research into novel, patient-centered, and mechanism-driven strategies for hyperlipidemia treatment. The aim of this review is to examine the relationship between pathological lipids and burgeoning biomaterials-based, nonsurgical, and minimally invasive therapeutic modalities for hyperlipidemia. By converging knowledge from lipids, biomaterials, and interventional therapeutics, this review seeks to emphasize novel treatment modalities that may reset and rethink hyperlipidemia therapy and, in turn, translate into better long-term cardiovascular outcomes.

## 1. EMERGING BIOMATERIAL

### 1.1 Lipid based Nano Carriers:

Hyperlipidemia is a metabolic disorder that poses a threat to cardiovascular disorders and is triggered due to the accumulation of excess lipids like cholesterol and triglycerides within the blood and tissues. The major drawback associated with the treatment of hyperlipidemic patients is that present drugs have poor solubility, bioavailability, and severe disadvantages due to potential side effects. Lipid-based nanocarriers that have enhanced drug delivery properties and also influence lipid metabolism include liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs).[10] Lipid-based nanocarriers such as liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) have gained serious attention for treating hyperlipidemias due to similarity in size to natural lipoproteins and selectivity towards lipid metabolism tissues.[10,11] Liposomes are phospholipid bilayer vesicles that are highly similar to cellular membranes, which facilitates effective interaction with LDL receptors and scavenger receptors on hepatic cells [12]. Liposome-encapsulated lipid-lowering agents display increased hepatic uptake by ApoE-mediated endocytosis, which leads to enhanced cholesterol efflux and reduced plasma LDL levels [13]. The aqueous core and lipid bilayer structure of liposomes facilitate simultaneous delivery of hydrophilic and lipophilic drugs, which favour multitargeting lipid metabolism modulation [12]. SLNs are solid lipid nanoparticles that are reinforced by surfactants to facilitate controlled drug delivery and increased stability compared to liposomes [10]. The lipid nature of SLNs facilitates selective interaction with CD36 receptors and SR-B1 receptors on adipocytes and macrophages that are implicated in lipid storage and foam cell formation [14]. The delivery of lipid-lowering drugs by SLNs inhibits adipogenesis and hepatogenesis by modulating the transcription factors PPARγ and SREBP-1c [15]. NLCs are

second-generation nanoparticles with a solid and liquid core, forming a heterogeneous structure in lipids, thus forming a porous structure, which increases the drug loading and inhibits the earlier diffusion of drugs [11]. NLCs possess a higher circulation phase and tissue distribution, and they promote higher uptake through the LDL and ApoE pathways in hepatocytes and adipocytes, respectively due to increased interaction with LDLR and ApoE receptors in target cells. They display a higher rate of intracellular drug delivery, thus causing a sustained inhibition of lipid accumulation and a higher oxidative metabolism of fatty acids [16]. The combined uptake and intracellular drug delivery of lipids in the form of nanocarriers promotes a lowered plasma TG levels, reduced adipocyte size, decreased hepatocyte accumulation, and normalization of lipid levels, respectively [15, 17].

**1.2 Polymeric Nano Carriers**

Due to the sustained drug release and adjustable degradation rate, poly(lactic-co-glycolic acid) (PLGA) is a biocompatible and biodegradable polymer and is utilized increasingly as a controlled-drug-delivery system for lipid-lowering drugs.[18] PLGA nanoparticles prevent the degradation of the enclosed drugs both chemically and enzymatically following their oral or parenteral administration and hence increase their circulation half-life and systemic availability.[19] The sustained release profile of PLGA nanoparticles has reduced the adverse effects of lipid-lowering drugs systemically since their availability has been enhanced and frequency of doses has been reduced.[21] In a hyperlipidemic state, PLGA nanoparticles selectively concentrate in lipid metabolism-acting organs such as the liver and lipid tissue and regulate lipid homeostasis.[22] Low-density lipoprotein receptors (LDLR), scavenger receptors, and liver-specific asialoglycoprotein receptors (ASGPR) are also involved in the receptor-mediated endocytosis of PLGA nanoparticles in hepatocytes, which helps in the clearance of cholesterol from the liver as well as in lipid metabolism regulation.[19, 22] Inhibition of lipogenesis in the liver occurs due to the intracellular trafficking of PLGA nanoparticles to the endosomal and lysosomal membranes, resulting in the breakdown of polymers and regulated intracellular releases of lipid-lowering drugs.[22] In view of their own inherent cationic charge, biodegradability, and biocompatibility, chitosan nanoparticles have gained relatively greater importance in the management of metabolic disorders, such as hyperlipidemia.[20] Chitosan nanoparticles' mucoadhesive attributes along with positive charges help in the increased permeability of the intestines, resulting in the substantial increase in bioavailability and oral absorption of lipid-lowering drugs.[20, 21] Chitosan nanoparticles show enhanced interaction with negatively charged cell membranes in a hyperlipidemic condition, resulting in encouraging preferential targeting in the case of both adipose tissues and the liver.[20] In adipocytes, the endocytosis of chitosan-based nanoparticles is mediated by mechanisms such as insulin receptor-mediated pathways, fatty acid translocase/CD36, and PPAR_gamma-associated pathways, all of which can be modified as desired for influencing fatty acid uptake or adipogenic differentiation.[22] The intracellular drug delivery of lipid-lowering agents because of receptor-mediated endocytosis of chitosan-based nanoparticles has stimulated the inhibition of adipogenesis and lipogenesis, promotion of lipolysis, as well as inhibition of adipocyte hypertrophy.[20, 22] The intracellular delivery of the lipid-lowering drugs from PLGA and chitosan-based nanocarriers has accelerated the efflux of cholesterol mediated by the enhanced expression of ATP-binding cassette transporters, such as ABCA1 and ABCG1.[22] In aggregate, these pathways have contributed to lowering plasma lipid levels, mitigating lipids accumulation, as well as reducing the associated metabolic disorders of hyperlipidemia.[22]

**1.3 Inorganic Nano Carriers**

They possess high cellular uptake efficiency and intrinsic bioactivity, making them very effective inorganic nanocarriers for the management of metabolic disorders, including hyperlipidemia.[23] Following systemic administration, AgNPs primarily accumulate within organs responsible for lipid metabolism, such as the liver and adipose tissue.[24] In hepatocytes, AgNP uptake occurs majorly through scavenger receptors and LDL receptor-mediated endocytosis, enhancing hepatic lipid clearance.[24,25] In adipocytes, AgNPs modulate PPARγ-associated pathways, leading to suppression of adipogenic differentiation and reduced formation of lipid droplets. Non-Surgical and Minimal Invasive Therapies [25] Intracellular activity mediated by AgNP decreases triglyceride synthesis and plasma lipid levels under hyperlipidaemic conditions. [24] Gold nanoparticles are biocompatible, chemically stable, and easily functionalized, which allows receptor-specific targeting of disorders in lipid metabolism.[26] AuNPs efficiently accumulate in the liver through the LDLR and ASGPR, facilitating hepatocyte-specific uptake.[27] In adipose tissue, AuNPs interact with insulin receptors and CD36, resulting in changes in fatty acid uptake and enhanced lipolysis.[27,28]PPARγ and SREBP-1c down regulation inhibit AuNPs adipogenesis. Altogether, these mechanisms contribute to the reduction of hepatic steatosis and improvement of lipid profiles. [28,27] Iron oxide nanoparticles present superparamagnetic properties and are vastly explored for their theranostic applications in metabolic disorders.[29]The majority of IONPs are internalized by hepatocytes through scavenger receptors and transferrin receptor-mediated endocytosis.[30] In adipocytes, iron oxide nanoparticles alter insulin signaling cascades to increase glucose uptake as well as lipolysis.[31] IONPs control lipid metabolism by activating the AMP-activated protein kinase (AMPK), which suppresses lipogenesis and activates fatty acid oxidation.[31] On a whole, iron oxide nanoparticles inhibit lipid accumulation and correct lipid homeostasis.[29]

## 2. NON-SURGICAL AND MINIMAL INVASIVE THERAPIES

### 2.1 Gastric Balloons

A gastric balloon, or intragastric balloon, is an MSA treatment used for weight loss through the implantation of the balloon within the stomach to take up space, causing you to feel the full effect of food much earlier with much smaller portions, resulting in fewer calorie consumption levels and utilized for only 6-12 months in patients with obesity when other weight reduction techniques were unsuccessful. The saline or air-filled balloon occupies a volume of about 400-700 mL within the stomach, significantly limiting the space available for food and thus inducing a high sensation of fullness. Stimulation of the stomach walls' gastric receptors, or rather mechanoreceptors, occurs due to this mechanical distension [32, 36]. The afferent vagal fibers transmit signals of stomach distension to the hypothalamus, which inhibits eating and excites a sensation of satiety [33, 37]. The role of balloons is known to influence ghrelin, a peptide hormone responsible for promoting eating and largely secreted by cells in the stomach's fundus. The diminished secretion or expression of ghrelin cells post balloon insertion is suspected in some studies to reduce the drive for feeding [34, 38]. Adipocytes secrete leptin, a hormone that inhibits eating and indicates grapelike adequacy of energy. Leptin is known to reduce with weight loss, as indicated by a reduction in lipid mass [35][38]. Improved insulin sensitivity, reduction in triglyceride content, and enhanced lipid profiles are associated with weight reduction and hormonal imbalance. Decreased food uptake, enhanced satiety, and neurohormonal factors combined reduce body fat, which can improve cholesterol secretion (decreases in triglycerides; improved lipid metabolism) and other related metabolic criteria [35][39].

### 2.2 Endoscopic Sleeve Gastroplasty

Endoscopic Sleeve Gastroplasty (ESG) is a minimally invasive weight loss surgery that involves using the endoscope with a suturing tool passed through the mouth to go into the stomach and decrease its size by as much as 70% by making the stomach small, like a sleeve, without cutting or removing part of the stomach. During ESG-induced reduction of stomach volume, stretch-sensitive mechanoreceptors are activated. As a result, the release of hormones that promote satiety and delay gastric emptying, such as GLP 1 and PYY, becomes more frequent, which reduces caloric intake.[40] Catecholamine's bind to the β-adrenergic GPCRs of the adipocytes, raising cAMP, which in turn activates protein kinase A (PKA), phosphorylates hormone-sensitive lipase (HSL), and breaks down triglycerides into free fatty acids. This is indirectly enhanced by ESG through the creation of a negative energy balance [41]. A nuclear receptor called PPARγ regulates fat storage. Calorie restriction and reduced insulin levels ensuing from ESG suppress adipogenesis and promote fatty acid oxidation due to downregulation of PPARγ activity [42]. Leptin Secreted from adipocytes; regulates satiety and expenditure. Circulating leptin falls with weight loss due to ESG; improves sensitivity to leptin, decreases inflammation, and increases lipid metabolism. [43]Anti-inflammatory adipokine; rises with fat reduction and increases insulin sensitivity and oxidation of fatty acids. Adiponectin and leptin sensitivity improve glucose and lipid metabolism and decrease inflammation. GPCR agonism, PPARγ downregulation, and adipokine signaling improve metabolism and lipid profiles and decrease fat. These modulate and decrease fat and improve lipid profiles and metabolism due to hyperlipidemia. [44]

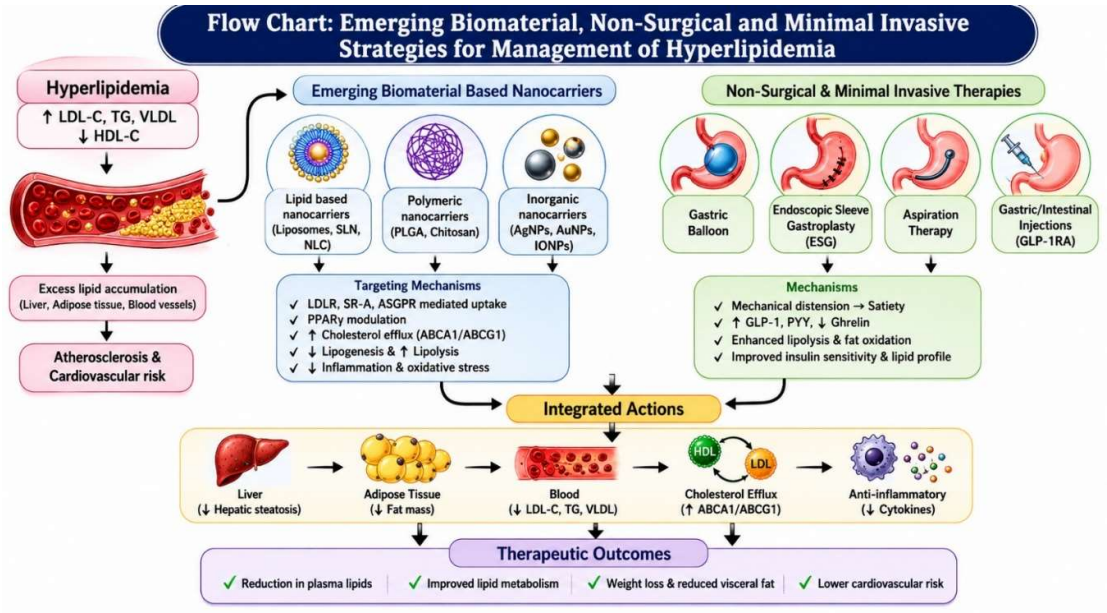
### 2.3 Aspiration therapy

An endoscopic weight-loss treatment for severe obesity allow to drain calories about 30% and promotes weight loss. Adipocytes are the main fat storage cells. In the presence of catecholamine interaction with beta-adrenergic receptors, there is an increase of intracellular cyclic AMP, leading to the activation of protein kinase A (PKA). PKA phosphorylates hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL), increasing triglyceride hydrolysis (lipolysis) into free fatty acids (FFA) and glycerol, which are secreted into the bloodstream for oxidation or re-esterification in another cell[45].Low density lipoprotein receptors (LDL R) on hepatocytes and target tissue cells accept LDL particles for removal of excess cholesterol from the blood. Scavenger receptors (e.g., CD36, SR-A) on macrophages and adipocytes accept modified lipoproteins for uptake, leading to foam cell formation seen in dyslipidemia if not properly regulated [46]. The ATP-binding cassette transporter (ABCA1/ABCG1) on adipocytes and macrophages promotes cholesterol efflux to high-density lipoproteins (HDL). The SR-B1 receptor mediates selective HDL cholesterol uptake in the liver, thereby completing reverse cholesterol transport (RCT), which is involved in systemic lipid lowering [47]. During conditions of lipid accumulation, macrophages migrate into adipose tissue and promote FFA and lipoproteins uptake via Cd36 and toll-like receptors (TLRs), leading to lipid accumulation and modulating inflammatory responses [48].

### 2.4 Gastric injections

Gastric injection delivers medicine directly into stomach cavity often using endoscope they act as GLP 1 receptor agonist (GLP 1RA) and interacts with the GLP 1R, a G protein coupled receptor found in major target tissues, to trigger a cascade of intracellular events, including cAMP, PKA, and PI3K/Akt signaling pathways [49]In the hypothalamus, GLP 1R stimulation suppresses appetite and hunger, produces satiety, and slows down gastric emptying, resulting in reduced caloric and indirect reduction in adipose tissue. On pancreatic β cells, GLP 1RA stimulates insulin release and inhibits the secretion of glucagon in a glucose concentration dependent manner, thus modulating glucose and lipid levels in the body, hence facilitating reduced fat storage in peripheral tissues. Signaling by GLP 1R is associated with optimizing adipose tissue distribution and reduction in both visceral and subcutaneous adipose tissues. Clinical trials reveal a significant reduction in both major and minor adipose depots with GLP 1RA administration

[50]. Furthermore, GLP 1 could modulate the metabolism of adipocytes and induce properties related to the genesis or browning, hence facilitating the preference for lipid oxidation instead of storage [51] Though there is low expression of GLP-1R in hepatocytes, GLP-1RAs have been shown to hav2e an indirect effect on lowering hepatocellular fat content by enhancing insulin signaling, decreasing lipogenesis, and decreasing VLDL secretion, which helps in lowering hyperlipidemia. This is due to the comprehensive effect on appetite regulation, insulin/glucagon balance, and fat metabolism in adipose tissues and the liver; therefore, weight loss, abdominal fat, lipid levels, and hyperlipidemia [52]




**Comparative Summary**

**Table 1. Nanocarriers**

| Nanocarriers | Target | Mechanism | Advantages | Limitations |
|---|---|---|---|---|
| Liposomes | LDLR | Enhanced hepatic uptake | Biocompatible | Stability issues |
| SLNs | CD36 | Controlled release | Improved stability | Low drug loading |
| NLCs | ApoE | Sustained delivery | High bioavailability | Complex formulation |

**Table 2. Minimal Invasive Therapies**

| Therapy | Mechanism | Lipid Effect | Advantages | Limitations |
|---|---|---|---|---|
| Gastric Balloon | Satiety induction | Reduced TG | Non-surgical | Temporary discomfort |
| ESG | Reduced stomach volume | Improved metabolism | Minimally invasive | Requires expertise |
| GLP-1 Injection | Hormonal modulation | Fat oxidation | Metabolic improvement | High cost |

## CONCLUSION

The combined advancements of nanocarriers with highly minimally invasive techniques mark the beginning of a new dawn in treating hyperlipidemias by overcoming many obstacles that have bedeviled many treatments in specifically modulating this condition. Since these new advancements not only have been able to lower plasma lipids as well as adipose but have also significantly reduced invasiveness, it will be important to focus on translation to practice and cocktail therapy approaches in addressing the high prevalence of cardiovascular diseases. The treatment of hyperlipidemia is increasingly influenced by the integrations between novel biomaterials and non-invasive and minimally invasive therapies. Such a paradigm shift is trending from pragmatism focused on the quick achievement of clinical endpoints. Novel biomaterials such

as stimulus-responsive polymers, lipid nanocarriers, hydrogels, and bioengineered scaffolds will play a pivotal role in the treatment of hyperlipidemia since these biomaterials will be engineered to facilitate the targeted delivery of lipid-lowering agents, genes, peptides, or microbe modulating agents with enhanced bioavailability and decreased systemic toxicity. These biomaterials will be engineered to respond to the local physiological signals in the gastrointestinal tract, liver, or adipose tissue. Such an approach will permit the controlled release of the drug at the target site. Simultaneously, non-invasive procedures for the treatment of hyperlipidemia, namely bariatric procedures based on the use of an endoscopic approach, the use of gastric balloons, aspiration therapies, and the intra-gastric or intestinal injection of medications or newer agents will increasingly become bio-functional interfaces incorporating drug-releasing or cell-interaction biomaterials. Looking forward, the advancement of "cocktail" therapies that leverage the synergy of biomaterial delivery with other existing procedures, particularly in the area of endoscopic or catheter-based interventions, will be a key emphasis. Also on the horizon are the potential advancements in personalized or "stratified" therapies in which biomaterials will be designed in a way that is subject to the specific lipid profiles and genetic risks of the target patients. Another aspect is the advancement in biodegradable materials. More specifically, future studies on the topic will need to take a translational approach in order for the technology to advance from the stage of a proof-of-concept trial and become a reality. Indeed, the future directions suggested in this topic are promising in the way that biomaterial technology has the potential to treat hyperlipidemia in a way that is not pharmacological.

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