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Efficacy of Exosome-Derived microRNA Therapy versus GLP-1 Agonists in Improving Insulin Sensitivity among Obese Type 2 Diabetics: A Narrative Review

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance and hyperglycemia, with obesity being a major contributory factor through mechanisms involving inflammation, adipokine dysregulation, and ectopic lipid deposition. While GLP-1 receptor agonists such as liraglutide improve insulin sensitivity via enhanced insulin secretion, weight reduction, and anti-inflammatory effects, emerging exosome-derived microRNA (miRNA) therapies offer novel disease-modifying potential. Exosomes, nano-vesicles secreted by cells, carry miRNAs that modulate gene expression in recipient tissues. Preclinical studies demonstrated that targeted delivery of miRNAs such as miR-223 and anti-miR-29 improves insulin signaling pathways, reduces hepatic gluconeogenesis, and ameliorates adipose inflammation, leading to enhanced insulin sensitivity in obese diabetic models. This narrative review utilized an extensive literature search of PubMed and Google Scholar databases to compare the mechanistic rationale, efficacy, and translational challenges of exosome-derived miRNA therapies versus GLP-1 agonists in improving insulin sensitivity among obese type 2 diabetics. While GLP-1 agonists remain established therapies with demonstrated clinical benefits, exosome-derived miRNA therapies are still in preclinical development stages, facing challenges of manufacturing, targeting specificity, and regulatory approval. Future clinical trials and biotechnological advances are needed to translate these RNA-based therapies into effective treatments for metabolic disorders.

Keywords: Type 2 Diabetes Mellitus**,** Insulin Resistance**,** Exosome-Derived microRNA Therapy**,** GLP-1 Receptor Agonists**,** Metabolic Disease Treatment.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance, impaired insulin secretion, and hyperglycemia [1, 2]. Globally, its prevalence is increasing, largely driven by obesity and sedentary lifestyles [3]. Obesity, particularly visceral adiposity, is a major contributor to insulin resistance through mechanisms including adipokine dysregulation, chronic low-grade inflammation, and ectopic lipid accumulation [4]. Improving insulin sensitivity is thus a key therapeutic target in the management of obese T2DM patients to achieve optimal glycemic control and mitigate cardiovascular and metabolic complications.

Currently, glucagon-like peptide-1 (GLP-1) receptor agonists such as liraglutide and semaglutide are widely used in T2DM management [5, 6]. They enhance insulin secretion in a glucose-dependent manner, suppress glucagon, delay gastric emptying, and promote weight loss, collectively improving insulin sensitivity. However, limitations such as gastrointestinal side effects, injection burden, and high cost restrict their universal acceptance.

Recent advances in extracellular vesicle research have identified exosome-derived microRNAs (miRNAs) as potential therapeutic agents [7]. Exosomes are nano-sized vesicles secreted by various cell types, carrying bioactive molecules including miRNAs that regulate gene expression in recipient cells. Exosome-derived miRNAs such as miR-29, miR-

122, and miR-223 have been implicated in modulating insulin signaling pathways, lipid metabolism, and inflammatory processes associated with insulin resistance. Early preclinical studies suggest that targeted delivery of exosome-derived miRNAs can ameliorate insulin resistance and improve metabolic profiles. This narrative review critically evaluates the efficacy of exosome-derived microRNA therapy compared to GLP-1 agonists in improving insulin sensitivity among obese type 2 diabetics. It examines the mechanistic basis, preclinical and clinical evidence, therapeutic benefits, limitations, and translational challenges. This knowledge is essential to guide future research and clinical applications of innovative RNA-based therapies in metabolic disorders.

Pathophysiology of Insulin Resistance in Obese Type 2 Diabetics

Obesity-induced insulin resistance arises from complex interactions between metabolic, inflammatory, and hormonal factors [8]. Excess adipose tissue, particularly visceral fat, leads to increased release of free fatty acids (FFAs), pro-inflammatory cytokines (TNF-α, IL-6), and adipokines such as resistin, which impair insulin signaling pathways in peripheral tissues.

At the molecular level, elevated FFAs activate serine kinases such as protein kinase C (PKC) and c-Jun N-terminal kinase (JNK), leading to inhibitory phosphorylation of insulin receptor substrate (IRS) proteins [9]. This attenuates downstream PI3K/Akt signaling, reducing glucose uptake by skeletal muscle and adipose tissue. Moreover, ectopic lipid deposition in the liver and muscle exacerbates insulin resistance through lipotoxicity.

Chronic inflammation in obesity promotes macrophage infiltration into adipose tissue, further augmenting pro-inflammatory cytokine production and insulin resistance [10]. Therefore, therapeutic strategies targeting these molecular and inflammatory pathways hold promise in reversing insulin resistance and improving metabolic health in obese T2DM patients.

Mechanistic Basis of GLP-1 Agonists in Improving Insulin Sensitivity

GLP-1 is an incretin hormone secreted by intestinal L-cells in response to nutrient ingestion [11, 12]. GLP-1 receptor agonists mimic endogenous GLP-1 actions by:

i. Enhancing glucose-dependent insulin secretion from pancreatic beta cells.
ii. Suppressing glucagon secretion, reducing hepatic glucose output.
iii. Slowing gastric emptying, attenuating postprandial glucose excursions.
iv. Promoting satiety and weight loss, which indirectly improves insulin sensitivity.

GLP-1 receptor activation in peripheral tissues such as adipose tissue and skeletal muscle also enhances insulin signaling pathways. Studies have shown increased phosphorylation of IRS-1 and Akt, facilitating glucose uptake and utilization. Moreover, GLP-1 agonists exert anti-inflammatory effects by reducing pro-inflammatory cytokine expression in adipose tissue and improving endothelial function.

Clinical trials have demonstrated significant reductions in HbA1c levels, body weight, and insulin resistance indices such as HOMA-IR with GLP-1 agonist therapy, establishing their role in T2DM management guidelines.

Exosome-Derived microRNA Therapy: Mechanistic Rationale

Exosomes serve as natural carriers of miRNAs, mediating intercellular communication by transferring genetic information to recipient cells [13]. miRNAs are small non-coding RNAs that regulate gene expression post-transcriptionally by binding to complementary sequences in target mRNAs, leading to mRNA degradation or translational repression [14]. Therapeutic strategies involve either inhibiting deleterious miRNAs or supplementing beneficial miRNAs using exosome-based delivery systems. Exosomes provide a biocompatible, stable, and targeted delivery vehicle, enhancing therapeutic efficacy while minimizing off-target effects. In the context of insulin resistance, specific exosome-derived miRNAs have been implicated in modulating key insulin signaling components:

i. **miR-29 family**: Negatively regulates insulin signaling by targeting IRS-1 and PI3K subunits, contributing to insulin resistance. Inhibition of miR-29 improves insulin sensitivity in preclinical models.
ii. **miR-122**: Elevated in obese and insulin-resistant states, modulating hepatic lipid metabolism and insulin sensitivity. Targeted silencing reduces hepatic glucose production and improves insulin action.
iii. **miR-223**: Exhibits anti-inflammatory effects and improves insulin sensitivity by suppressing NLRP3 inflammasome activation [15].

Comparative Efficacy: Exosome-Derived microRNA Therapy versus GLP-1 Agonists

i. **Improvement in Insulin Sensitivity:** Clinical studies report significant improvements in insulin sensitivity markers. For example, treatment with liraglutide has shown a 30-40% reduction in HOMA-IR and increased glucose disposal rates in euglycemic clamp studies [16]. The effects are mediated by weight loss, direct insulinotropic actions, and anti-inflammatory properties. Preclinical studies in obese diabetic mice have demonstrated that exosome-mediated delivery of miR-223 and anti-miR-29 enhances insulin sensitivity by restoring IRS-1/Akt signaling, reducing hepatic gluconeogenesis, and ameliorating adipose tissue inflammation. Improvements in insulin sensitivity indices and glucose tolerance have been observed,

often comparable or superior to pharmacological agents. However, human clinical data remain sparse, and efficacy in large-scale trials is yet to be established.

ii. **Effects on Weight and Adiposity:** Induce significant weight loss (mean 3-6 kg) via appetite suppression and delayed gastric emptying, which contributes to improved insulin sensitivity and metabolic parameters. Effects on weight reduction are indirect, mediated by improved metabolic function and reduced inflammation rather than appetite modulation. Current preclinical studies have not demonstrated significant weight loss as a primary outcome.

iii. **Anti-Inflammatory and Metabolic Benefits:** Both interventions reduce systemic and adipose tissue inflammation, enhancing insulin signaling. GLP-1 agonists decrease circulating pro-inflammatory cytokines, while exosome-derived miRNAs directly modulate inflammatory pathways and immune cell phenotypes in adipose tissue.

iv. **Safety and Side Effects:** Common side effects of include nausea, vomiting, and diarrhea [17]. Rare risks involve pancreatitis and gallbladder disease. Preclinical studies report minimal toxicity and immunogenicity, given exosomes' biocompatibility. However, potential risks include unintended gene silencing, off-target effects, and challenges in ensuring dose consistency and biodistribution.

v. **Delivery and Administration:** Administered via daily or weekly subcutaneous injections, posing adherence barriers for some patients. Potential for intravenous or targeted tissue-specific administration. Advances in exosome engineering may enable non-invasive delivery modalities in the future.

Translational Challenges and Future Directions

Despite promising preclinical results, several challenges impede clinical translation of exosome-derived microRNA therapies:

i. **Manufacturing and Standardization:** Scalable production of clinical-grade exosomes with consistent miRNA content and therapeutic potency is technically demanding [18].

ii. **Targeting Specificity:** Ensuring efficient delivery to insulin-sensitive tissues (liver, muscle, adipose tissue) without off-target accumulation requires precise engineering [19].

iii. **Safety and Off-Target Effects:** Comprehensive toxicological assessments are needed to rule out unintended gene regulation, immune reactions, or tumorigenicity.

iv. **Regulatory Hurdles:** As novel biologic therapies, regulatory frameworks for exosome-based miRNA therapies are evolving, necessitating robust preclinical and phased clinical trial data [20].

v. **Cost-Effectiveness and Accessibility:** High production costs may limit widespread adoption, emphasizing the need for cost-reduction strategies and equitable access models.

Future research should focus on:

i. Conducting well-designed Phase I/II trials to evaluate safety, pharmacokinetics, and efficacy in humans.

ii. Developing advanced exosome engineering platforms for enhanced targeting and therapeutic loading.

iii. Elucidating miRNA-mediated signaling networks to identify optimal therapeutic targets for insulin resistance.

iv. Exploring combination therapies integrating exosome-based miRNAs with existing pharmacologic agents for synergistic metabolic benefits.

CONCLUSION

Exosome-derived microRNA therapy represents a novel and promising approach to improving insulin sensitivity in obese type 2 diabetics by targeting fundamental molecular and inflammatory pathways of insulin resistance. Preclinical studies demonstrate its ability to restore insulin signaling, reduce hepatic gluconeogenesis, and ameliorate adipose tissue inflammation, potentially achieving outcomes comparable to or surpassing those of GLP-1 receptor agonists. In contrast, GLP-1 agonists remain established therapies with proven efficacy in enhancing insulin sensitivity, reducing weight, and improving glycemic control, albeit with side effects and adherence challenges. However, the translation of exosome-based miRNA therapies into clinical practice faces significant hurdles, including manufacturing standardization, targeted delivery optimization, safety validation, and regulatory approval pathways. Until these challenges are addressed, GLP-1 agonists will continue to be the mainstay pharmacologic intervention for improving insulin sensitivity in obese T2DM patients. Nonetheless, exosome-derived miRNA therapies hold the potential to revolutionize metabolic disease treatment, offering personalized, targeted, and disease-modifying benefits. Collaborative interdisciplinary efforts integrating molecular biology, bioengineering, clinical medicine, and regulatory science will be essential to unlock their full therapeutic potential in the coming decade.

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