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# Cell-Free Therapeutic Mechanisms of AD-MSC Secretome in Type 2 Diabetes Mellitus: Literature Review

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**Abstract:** Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder with a globally increasing prevalence, while conventional therapies often fail to halt disease progression. The secretome derived from adipose-derived mesenchymal stem cells (AD-MSCs) holds great potential as a cell-free therapy strategy, as it contains various bioactive molecules, cytokines, and extracellular vesicles that regulate glucose metabolism and modulate immune responses. This review discusses the molecular components of AD-MSC secretome, its mechanisms in enhancing insulin sensitivity and protecting pancreatic β-cells, as well as the challenges in its clinical application. Based on literature from 2018–2025 in PubMed, Scopus, and Web of Science, AD-MSC secretome has been shown to enhance IRS-1 phosphorylation, activate the PI3K/Akt pathway, and promote GLUT4 translocation while suppressing chronic inflammation. Growth factors (HGF, IGF-1, VEGF) and microRNAs (miR-126, miR-21, miR-146a) contribute to β-cell regeneration. Donor variability, culture conditions, and isolation methods affect secretome quality, which can be optimized through preconditioning or genetic modification.

**Keywords:** Secretome, Adipose-Derived Mesenchymal Stem Cell, Cell-Free Therapy, Insulin Resistance, β-Cell Regeneration, Type 2 Diabetes Mellitus

## Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from a combination of peripheral insulin resistance and pancreatic β-cell dysfunction. Globally, T2DM has become one of the leading causes of cardiometabolic morbidity and mortality. Its rapidly increasing prevalence, driven by obesity, sedentary behavior, and dietary transitions, poses a major global health challenge. The multifactorial nature of T2DM pathogenesis underscores the urgent need for therapeutic strategies that not only control blood glucose levels but also target the underlying mechanisms of β-cell deterioration and insulin resistance (Zeinhom, 2024).

In recent years, regenerative medicine has offered new perspectives in the management of metabolic diseases, including diabetes mellitus. Among various approaches, mesenchymal stem cell (MSC)-based therapies have demonstrated potential to restore tissue homeostasis through their paracrine effects rather than direct cellular replacement. The MSC secretome, consisting of a wide range of bioactive components such as cytokines, chemokines, growth factors, peptides, and extracellular vesicles (EVs/exosomes), has emerged as a promising cell-free therapeutic strategy. This secretome has been reported to exert anti-inflammatory, antioxidative, anti-apoptotic, and pro-angiogenic effects, thereby enhancing β-cell survival and improving systemic glucose homeostasis (Jiao, 2024). Compared to cell transplantation, secretome-based therapy offers advantages in safety, scalability, and regulatory feasibility.

Despite encouraging preclinical data, the therapeutic application of MSC-derived secretome in T2DM remains constrained by several limitations. Biological heterogeneity arising from donor variability, culture

conditions, and secretome harvesting methods contributes to inconsistent therapeutic outcomes. Furthermore, the absence of standardized characterization, dosage determination, and administration protocols hampers reproducibility and clinical translation. Discrepancies also persist in identifying key molecular constituents and dominant mechanisms of action that mediate metabolic improvements. These knowledge gaps highlight the necessity for a comprehensive synthesis of current evidence to delineate the translational potential of MSC secretome in diabetes therapy.

Among different tissue sources, adipose-derived mesenchymal stem cells (AD-MSCs) represent an advantageous candidate due to their abundance, minimally invasive isolation procedure, and robust secretory profile enriched in metabolic and immunomodulatory factors. Emerging evidence suggests that the AD-MSC secretome ameliorates hyperglycemia, improves insulin sensitivity, and promotes β-cell protection and regeneration without the risks associated with viable cell administration (Yan et al., 2024; Zhou et al., 2024). Therefore, this review aims to (1) delineate the molecular composition of the AD-MSC secretome relevant to T2DM pathophysiology, (2) elucidate the mechanisms underlying insulin resistance improvement and β-cell regeneration, (3) summarize current preclinical and clinical evidence, and (4) highlight ongoing challenges, technological advancements, and future research directions. By integrating molecular, experimental, and translational perspectives, this review seeks to establish a scientific foundation for the development of AD-MSC secretome-based cell-free therapy as a novel and effective approach for the treatment of type 2 diabetes mellitus.

## Materials and Methods

A systematic literature search was conducted in three major scientific databases, namely PubMed/MEDLINE, Scopus, and Web of Science. The combination of keywords used included "adipose-derived mesenchymal stem cells," "secretome," "type 2 diabetes mellitus," "insulin resistance," and "beta-cell regeneration." The search was limited to articles published between 2018 and 2025 to ensure data currency, and only English-language articles were included. Articles that met the criteria included original research (in vitro, in vivo, or clinical trials) as well as systematic or narrative review articles discussing the role of secretome or its derivatives, such as exosomes and paracrine factors from adipose-derived mesenchymal stem cells (AD-MSCs), in the context of the pathophysiology and treatment of type 2 diabetes mellitus (T2DM). Meanwhile, articles focusing on MSCs from non-adipose sources without relevance to T2DM, those not undergoing peer review, or single case reports with limited mechanistic data were excluded from consideration.

## Results and Discussion

The secretome of adipose-derived mesenchymal stem cells (AD-MSCs) is a complex collection of bioactive molecules secreted by MSCs derived from adipose tissue. Its main components include proteins and growth factors, cytokines and chemokines, extracellular vesicles (EVs) and exosomes, and non-protein molecules such as microRNA (miRNA) and mRNA. The composition and characteristics of this secretome are greatly influenced by donor variability, culture conditions (2D or 3D), preconditioning strategies, and the isolation method used. The following is a summary of bioactive molecules commonly found in the AD-MSC secretome:

**Table 1.** Major bioactive components in the AD-MSC secretome and their functions in type 2 diabetes melitus

| Bioactive Component | Primary Function in T2DM or Metabolic Dysfunction |
|---|---|
| miR-126 (IN MSC exosome) | Reduces inflammation caused by hyperglycemia, improves blood vessel response, and improves metabolic homeostasis (Zhang, 2019). |
| miR-125b (exosome MSC) | Protective effect on the kidneys (diabetic nephropathy) via TRAF6/Akt regulation, reducing kidney cell apoptosis (Cai et al., 2021). |

| Bioactive Component | Primary Function in T2DM or Metabolic Dysfunction |
|---|---|
| FGF21 (from modified MSCs | Improves glucose and lipid metabolism, enhances β-cell function, and lowers blood glucose levels in a DMT2 mouse model (Xue, 2021). |
| TGF-β1 (stimulation in AD-MSC / secretome effects) | Immune modulator and cytokine/chemokine secretion regulation; in a review study, TGF-β1 exposure modulated the cytokine-chemokine profile of ASCs, including immunomodulatory capacity (Ademi et al., 2023). |
| Protein & growth factor-ke healing (VEGF, HGF, EGF, KGF, IGF-1, etc.) | Supports healing, angiogenesis, cell proliferation and regeneration of damaged tissue, as well as tissue structure repair; also relevant for micro and vascular tissue in DMT2 (Ademi, 2023; Li, 2024). |

## Variations in Culture Conditions and Their Effects on Secretome Composition

Culture conditions play an important role in determining the composition and biological potential of the secretome of adipose-derived mesenchymal stem cells (AD-MSCs). A comparison between two-dimensional (2D) and three-dimensional (3D) cultures shows significant differences in the molecular profiles produced. A study titled "Characterization of the Secretome from Spheroids of Adipose-Derived Stem Cells (SASCs)" reports that AD-MSCs cultured in 3D spheroids produce extracellular vesicles (EVs) and exosomes with higher expression of angiogenic microRNA (miR-126), immunomodulatory (miR-146a), and stemness genes such as NANOG and SOX2, compared to conventional 2D cultures (Urrata, 2024). Additionally, preconditioning treatments such as exposure to hypoxic conditions, oxidative stress, or specific environmental stimulation have also been shown to influence secretome characteristics. Although research specifically assessing the effects of preconditioning on AD-MSCs in the context of type 2 diabetes mellitus (T2DM) is still limited, a number of studies on MSCs from various sources show that this approach can increase growth factor production, the number of exosomes, and strengthen the immunomodulatory capacity of the secretome (Padinharavil, 2024).

## Techniques and Methods for Secretome Isolation and Characterization

The process of isolating and characterizing the secretome, particularly exosomes or EVs from AD-MSCs, is carried out using several technical approaches. Commonly used isolation methods include ultracentrifugation, size exclusion chromatography, immunoaffinity capture, or a combination of these techniques. In general, exosomes are extracted from conditioned medium after a certain culture period, for example, after cells reach optimal confluence or receive specific stimulation. Secretome characterization is performed to assess both physical and molecular aspects. Analysis of EV/exosome size and morphology generally uses Dynamic Light Scattering (DLS) or Electron Microscopy (Urrata, 2024). Surface markers such as CD63, CD81, and CD9 are evaluated through Western blot or flow cytometry. Meanwhile, the molecular profile of the secretome can be analyzed through proteomic or transcriptomic approaches, including microRNA and mRNA quantification using real-time PCR, next-generation sequencing, or other omics platforms (Advani et al., 2025).

## Important Characteristics of AD-MSC Secretome for DMT2 Therapy Applications

Several key characteristics of the secretome of adipose-derived mesenchymal stem cells (AD-MSCs) need to be considered in order to optimize their use as a therapy for type 2 diabetes mellitus (T2DM). One of the main factors is the dose and dosing regimen, as there is currently no standard regarding the effective protein concentration or number of exosomes to produce an in vivo biological response, such as improved blood glucose levels or pancreatic β-cell regeneration. In addition, stability and storage conditions are also important aspects. Although exosomes are known to be more stable than living cells, their biological activity can decrease due to variations in storage temperature, buffer type, or repeated freeze–thaw cycles. The next factor is the delivery strategy to the target tissue, which determines the effectiveness of the therapy. Secretomes can be administered

systemically or locally, for example, targeted directly to the pancreas, with or without the aid of delivery systems such as carriers or biomaterial scaffolds. Finally, the safety profile must be thoroughly evaluated. Although secretomes are generally low immunogenic, potential risks remain, including the possibility of fibrosis induction due to excessive TGF-β exposure or negative interactions in patients with certain comorbidities. Thus, optimization of dosage, stability, route of administration, and safety are crucial steps in the development of AD-MSC secretomes as an innovative therapy for DMT2.

**Table 2**. In vitro and in vivo studies on the effects of MSC secretome or exosomes (including AD-MSC) on insulin resistance and β-cells.

| Reference (year) | Model & Secretome Source | Key findings related to insulin resistance / β cells |
|---|---|---|
| Sun Y et al., 2018 | T2DM mouse model (HFD + STZ); exosomes from human umbilical cord MSC (hucMSC ex) | Lowered blood glucose, reduced β-cell apoptosis, improved IRS 1/Akt phosphorylation and GLUT4 expression improved insulin resistance |
| Jiao YR et al., 2024 | Summary of multiple studies: MSC-derived exosomes | MSC exosomes suppress pancreatic islet inflammation, increase insulin secretion, and improve insulin sensitivity in animal models; mechanisms include miRNA transfer and activation of the PI3K/Akt pathway |
| Gong X et al., 2024 | Summary of preclinical evidence (MSC) | MSC improves oxidative stress & inflammation, supports tissue repair and insulin sensitization in diabetes/obesity models |
| Kim JE et al., 2025 | MSC-derived exosomes for DM | Summarizes evidence that MSC-Exosome is effective in animal models of T1DM & T2DM including improvement in β cell function and increased insulin response. |
| Shi H et al., 2023 | In vivo obesity/IR model; bone marrow MSC derived exosomes | Activates the PI3K/Akt pathway and increases GLUT4 reduces obesity-induced insulin resistance. |
| Xia L et al., 2024 | PEGylated β cell-targeting MSC exosomes (modified) mouse model | Exosome target directed enhances delivery of contents (miRNA/protein) to β cells increases insulin secretion and lowers blood glucose. |
| Sun et al. 2018 | In vivo T2DM mice | Reduces β-cell destruction caused by STZ and increases plasma insulin levels. |
| Zeinhom A et al., 2024 | Review of hMSCs (various sources) in diabetes | Summarizes evidence that MSCs (including AD-MSCs) exert pleiotropic effects on metabolic and inflammatory parameters; confirms the paracrine/secretome role. |
| Sanap A et al., 2024 | In vitro: effect of AD-MSC secretome (from healthy donors) on adipose/osteo related cells | Secretome AD MSC from healthy donors can modulate TNF-α inflammatory signals and improve cell function impaired by metabolic conditions implications for improving metabolic profiles. |
| Kim B et al., 2024 | hWJMSC exosomes pada HFD-induced obese mice | Reduces adiposity and insulin resistance; improves adipose tissue inflammatory markers |
| Cui X et al., 2021 (landmark review & mechanistic studies) | MSC-exosome | Identification of miRNAs (miR-29b-3p, miR-126, miR-21, miR-146a) associated with modulation of insulin signaling, inflammation, and β-cell apoptosis. |
| Suhandi C et al., 2025 | Secretome/secretomebased therapies in in vivo studies (diabetes/woun d healing) | Meta-analysis shows improvement in diabetes wound therapy outcomes and several metabolic parameters; accumulated evidence supports the translational potential of secretome but highlights study heterogeneity. |

**Mechanism and Therapeutic Potential of AD-MSC Secretome in Type 2 Diabetes Mellitus**

In vitro research results show that the secretome and exosomes produced by AD-MSCs play a direct role in increasing glucose uptake by target cells, improving the expression of genes related to insulin sensitivity, and providing protection to pancreatic β cells. These findings reinforce the hypothesis that AD-MSC paracrine components are important mediators in glucose metabolism regulation. Based on the summary of studies presented in the previous table, secretome and exosomes derived from AD-MSCs have been shown to mediate various biological mechanisms that contribute to metabolic improvement in type 2 diabetes mellitus. These mechanisms can be further explained as follows.

**1. Increased Insulin Sensitivity**

Preclinical evidence shows that paracrine components of the MSC secretome including proteins and extracellular vesicles (EVs) or exosomes carrying miRNAs are capable of activating classical insulin signaling pathways (e.g., PI3K/Akt). Activation of this pathway improves IRS-1 phosphorylation and increases GLUT4 translocation in peripheral tissues such as skeletal muscle and adipose tissue, which ultimately lowers blood glucose levels in T2DM animal models. A number of in vivo studies have also reported improved metabolic function after administration of exosomes or conditioned medium derived from MSCs, consistent with increased PI3K/Akt activity and GLUT4 expression (Suhandi, 2025).

**2. Protection and Regeneration of Pancreatic β Cells**

The AD-MSC secretome contains various growth factors (e.g., HGF and IGF-1) and pro-survival molecules that support pancreatic β cell viability and function. These components have been shown to reduce apoptosis and increase insulin secretion in experimental models. In addition to protein factors, miRNA transfer via EVs also plays an important role in supporting the survival and regeneration of Langerhans islets. Several recent studies have shown that MSC exosomes can increase viability and insulin secretion function through activation of the PI3K/Akt pathway and suppression of pro-apoptotic signals (Trigo, 2025).

**3. Immunomodulation and Macrophage Phenotype Shift (M1 → M2)**

One of the most consistent therapeutic effects of MSC secretome is its ability to modulate the immune response of the microenvironment. The MSC secretome suppresses pro-inflammatory mediators such as TNF-α, IL-6, and NLRP3, while increasing anti-inflammatory cytokines such as IL-10 and TGF-β1. In addition, the secretome also promotes macrophage polarization towards the anti-inflammatory M2 phenotype. This mechanism is relevant to the pathogenesis of DMT2, as chronic inflammation in adipose tissue and the pancreas plays a major role in maintaining insulin resistance and β-cell dysfunction. Recent reviews provide strong evidence that the AD-MSC secretome plays a role in macrophage modulation and inflammasome suppression (Jiao, 2024).

**4. The Role of EVs/Exosomes and microRNAs as Functional Signal Carriers**

EVs and exosomes produced by MSCs carry cargo in the form of non-coding RNA (mainly miRNA) that can alter gene expression in target cells. Several miRNAs that are often associated with anti-diabetic effects include miR-126 (increases angiogenesis and insulin sensitivity), miR-21 (anti-apoptotic effect), and miR-146a (anti-inflammatory effect). miRNA transfer via exosomes is known to inhibit the NF-κB pathway, increase AMPK/Akt activity, and reduce oxidative stress, all of which contribute to improving insulin resistance and protecting β cells. Recent omics analyses have also mapped the miRNA profile in MSC-EVs, which consistently supports these effects (Zhou, 2024).

**5. Product Variability: Influence of Donor Source, Culture Conditions, and Isolation Methods**

Secretome heterogeneity is a critical issue in standardizing therapy. The composition and biological potential of the secretome are highly dependent on the MSC source (adipose, bone marrow, or umbilical cord), donor health status (e.g., reduced "stemness" in MSCs from T2DM patients), and culture conditions (2D vs. 3D, hypoxic preconditioning). In addition, EV isolation methods such as ultracentrifugation,

size exclusion chromatography, or immunoaffinity capture also affect the final results. This variability explains the differences between studies and poses a major challenge in the development of consistent therapeutic products. Therefore, comparative studies and standardization protocols are urgently needed (Wang, 2024).

## 6. Secretome Enhancement and Engineering Strategies for Clinical Applications

Engineering approaches such as hypoxic preconditioning, genetic modification of MSCs for FGF21 overexpression, or targeted exosome packaging have been shown to enhance secretome bioactivity and tissue targeting specificity. For example, MSCs modified to express FGF21 or exosomes paired with specific ligands for the pancreas demonstrated increased efficacy in diabetic animal models. Although these results are promising, comprehensive safety evaluations are required before they can be applied in human clinical trials (Kostecka, 2024).

## 7. Clinical Evidence and Translation Challenges

Although preclinical evidence strongly supports the potential of this therapy, clinical data on the use of AD-MSC secretome or exosomes in T2DM patients are still limited. Key challenges include the complexity of regulating biological products, long-term safety evaluation (particularly the risk of fibrosis due to excessive TGF-β activation), and the need for multicenter clinical trials with standardized protocols. Several recent reviews recommend a stepwise approach to clinical translation: standardization of production, dose safety testing, and efficacy testing in selected patient populations (Patt, 2024).

## 8. Recommendations for Further Research

To accelerate clinical translation, head-to-head studies comparing the AD-MSC secretome with other MSC sources in T2DM models are needed, as well as standardization of isolation and characterization methodologies (proteomics and miR-omics). The development of pharmacodynamic biomarkers to monitor the distribution and effects of the secretome in vivo is also important. In addition, controlled phase I/II clinical trials with standardized production protocols are a key step. The selection of appropriate donors and engineering techniques to improve the specificity and safety of the secretome should be the main focus of further research (Trigo, 2025).

## Conclusion

The secretome derived from adipose-derived mesenchymal stem cells (AD-MSC) shows significant potential as a cell-free therapeutic strategy for type 2 diabetes mellitus. Its bioactive components, including growth factors, cytokines, and extracellular vesicles, have been shown to enhance insulin sensitivity and protect pancreatic β-cell function. These findings indicate that AD-MSC secretome can modulate key pathological mechanisms of T2DM, supporting its development as a safe and effective alternative to cell-based therapy.

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