Diabetology & Metabolic Syndrome

REVIEW

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The therapeutic potential of mesenchymal stem cells-derived extracellular vesicles/exosomes on the diabetes: a systematic review study

Mahsa Kouhestani[1,2] and Asieh Hosseini[2*]

Abstract

Diabetes mellitus includes a wide range of chronic metabolic disorders that result in severe hyperglycemia and other damages in diabetic patients due to impaired insulin secretion or insulin inefficiency. This study purpose was to consider of the potential therapeutic properties of MSCs-derived EVs/Exo against DM. A complete systematic search was achieved in various electronic databases (Scopus, Web of Science, PubMed and Embase) up to June 2025, following the PRISMA guidelines. A whole of 89 studies were screened based on predetermined standards for inclusion and exclusion. Eventually, the current systematic study contained 13 publications that had the criteria of inclusion. According to the findings of this study, MSCs-derived EVs/Exo reduce DM and hyperglycemia with the high ability to regulate inflammatory-immune responses and activate autophagy pathways. However, compared to the diabetic groups, treatment with MSCs-derived EVs/Exo revealed tendency towards immunomodulatory, anti-inflammatory, anti-diabetic, regeneration and neogenesis of β-islets. In other studies, have been identified that DM causes significant biochemical changes in beta cells/pancreas tissue. In addition, obvious histological changes were observed in pancreatic tissue following DM. Generally, MSCs-derived EVs/Exo administration modulated most of the histological and biochemical changes caused by diabetes. Notably, the DM is improved through recovering damaged tissues, increasing insulin levels and glycemic stability. It seems that, MSCs-derived EVs/Exo exert these protective and therapeutic properties through the modulating of multiple mechanisms that are implicated in DM.

Highlights

- The efficacy of MSCs-derived EVs/Exo was confirmed by checking related studies results.
- Treatment with MSCs-derived EVs/Exo showed significant improvement in need to insulin and glycemic stability.
- The use of exosomes as natural drug delivery systems could be a new, cell-free therapeutic tool for diabetic patients.
- Exosome therapy, as a novel and efficient approach, could be a more suitable alternative to cell therapy in regenerative medicine.

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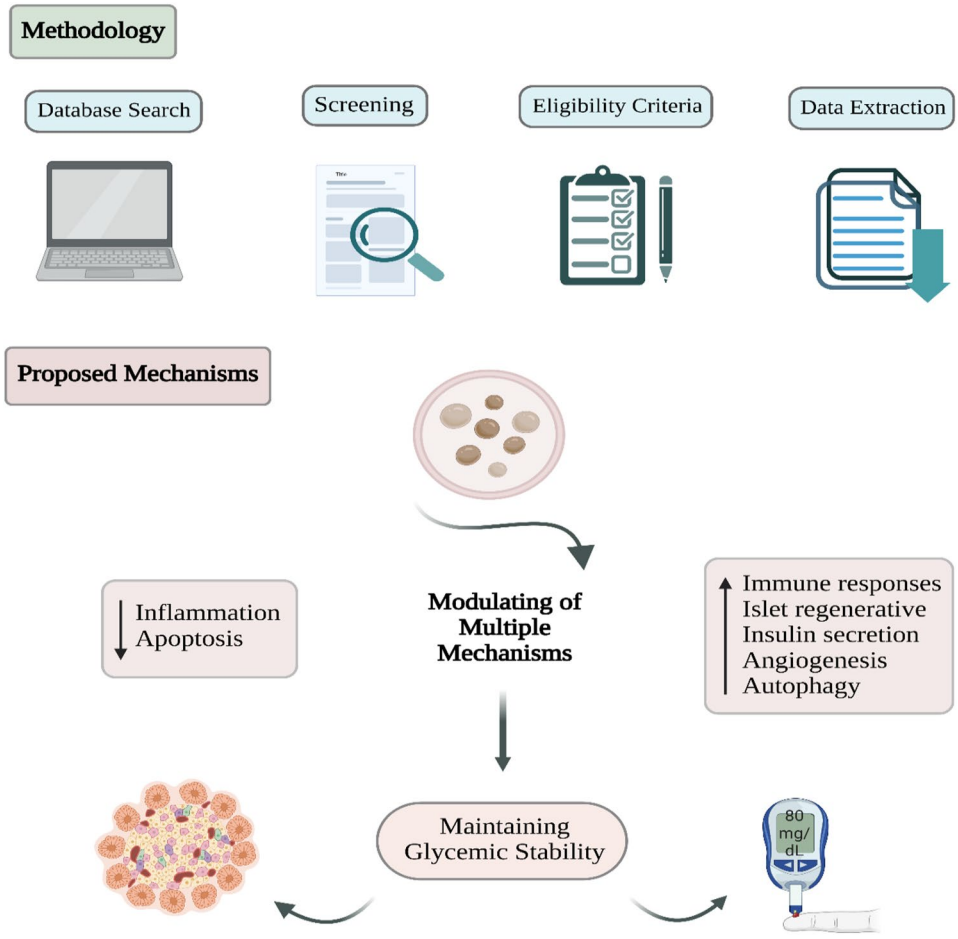
Keywords Diabetes mellitus. mesenchymal stem cells. extracellular vesicle. exosome. inflammation. apoptosis. signaling mechanisms

Graphical abstract



Introduction

Diabetes mellitus (DM) is a life-threatening disease and its prevalence is increasing worldwide [1]. According to the 9th edition of the Diabetes Atlas by the International Diabetes Federation (IDF), the global number of diabetic patients is estimated to be 463 million in 2019, which will increase to 578 million in 2030 and 700 million in 2040 [2, 3]. Also, diabetes is a major public health problem and a major health concern for the global population. According to the standards of the World Health Organization (WHO), diabetes is generally classified into two main types, type 1 diabetes (T1D) and type 2 diabetes (T2D) [4]. Both of these types cause severe hyperglycemia and many complications due to insulin secretion defects or insulin inefficiency [5]. Currently, diabetes has become a serious non-communicable disease that right next to cardiovascular diseases and malignant tumors causes a high mortality rate. Furthermore, with the emergence of the Covid-19 pandemic, according to numerous global statistics, the death rate in diabetic patients with Covid was much higher [6, 7].

Diabetic patients need external insulin injections to keep their blood glucose levels stable for a long time [8]. In this regard, diabetes specialists are studying and investigating treatment methods to optimize the treatment of diabetes, as well as searching for suitable alternative treatment strategies [9, 10]. Currently, cell-based therapeutic methods, including cell therapy, exosome (Exo) therapy, and gene therapy, have attracted the attention of scientists for the treatment of diabetes [11]. The main purpose of regenerative medicine is to repair and regenerate damaged tissues and improve their function in various human diseases [12]. For this purpose, various sources of cell therapy and cellular products are used in pre-clinical and clinical studies. One of the most important cellular products is exosome therapy, which

is a powerful tool for the development of therapeutic goals in regenerative medicine [13, 14]. According to the guidelines of the International Society for Extracellular Vesicles (ISEV), extracellular vesicles (EVs) have been proposed as a general term for particles that are naturally released from most cells into the extracellular space. The most important classification of EVs is based on biogenesis, which includes three main groups, microvesicles, apoptotic bodies and exosomes [15, 16]. Exosome, small secretory vesicles with a diameter of about 30–150 nm, which are made of multivesicular bodies [17, 18].

The main mechanism in causing diabetes, especially T1D, is the excessive activity of T helper immune cells and the infiltration of immune cells, which is accompanied by the high secretion of inflammatory cytokines and immune factors, which ultimately leads to apoptosis and destruction of pancreatic beta cells and defects in the production and secretion of insulin [19–21]. Studies have shown that mesenchymal stem cells (MSCs), and especially exosomes isolated from them, lead to beta cell regeneration and neogenesis through multiple mechanisms, including anti-inflammatory and immunomodulatory activities, protective and regenerative properties, antioxidant and anti-apoptotic effects [22, 23]. In fact, exosomes derived from MSCs can be suitable as a new therapeutic strategy for the treatment of inflammatory and autoimmune diseases such as diabetes due to their unique advantages such as regeneration of damaged tissue, less immunization, natural drug delivery systems, crossing biological barriers, prevention of transplant rejection, immune system modulation, and suppression of inflammatory mediators [17, 24, 25].

In this systematic study, we aimed to evaluate and analyze the potential therapeutic effects of MSCs-derived EVs/Exo against T1D and T2D in non-clinical studies and one clinical trial. Moreover, in this study was tried to response the following inquiries: (i) the underlying mechanisms of T1D and T2D, (ii) the protective role of MSCs-derived EVs/Exo against the harmful effects of DM on various organs, (iii) the fundamental mechanisms involved in the protective role of MSCs-derived EVs/Exo in DM. Finally, to achieve the above objectives, we executed a comprehensive literature review to investigate the protective role of MSCs-derived EVs/Exo in DM.

Methods

The current study summarizes the therapeutic potential of MSCs-derived EVs/Exo on the diabetes. The present systematic review was designed according to the PRISMA 2020 guideline (which include Preferred Reporting Items for Systematic Reviews and Meta Analyses) (Moheret al., 2009). Additionally, in this study was used from a PICO framework (Moher et al., 2009). These parameters include participants (P): DM (in vivo studies) and/or patients with adverse effects caused by diabetes (T1D, T2D) (clinical/in vivo studies); intervention (I): the treatment (MSCs-derived EVs/Exo administration); comparison (C): the comparison between (untreated/vehicle/alternative treatment); (O): there were two important outcomes: (1) changes in the T1D and T2D following diabetes treatment compared to control/non-treated groups and (2) changes in the DM (T1D, T2D).

Search strategy

We performed a comprehensive systematic search to identify all related studies on "the therapeutic potential of MSCs-derived-EVs/Exo on the diabetes disease" in both medical subject heading (MeSH) and advance in the PubMed, Web of Science, Scopus and Embase electronic databases from initiation until June 2025. The search of the present study was conducted using specific search terms: ("Diabetes Mellitus, Type 1" (MeSH) OR Autoimmune Diabetes (MeSH) OR Hyperglycemia (MeSH)) AND (Diabetes Mellitus, Type 2" (MeSH) OR "Diabetes Mellitus, Experimental" (MeSH)) AND ("Extracellular Vesicles" (MeSH) OR "Exosomes" (MeSH) OR "Cell-Derived Microparticles" (MeSH) OR "Stem cell-derived exosomes" (MeSH) OR "Stem Cell-Derived Extracellular Vesicles" (MeSH)).

Process of study selection

Criteria of the inclusion to this systematic review included the full text of scientific articles that met the following criterions: (1) all of them were written in English and published in recognized peer-reviewed journals; (2) they focused on the effects of MSCs-derived EVs/Exo in T1D and T2D (as specified by the keywords stated above); (3) they contained sufficient results; (4) there were no limitations on clinical trial, in vivo or in vitro studies in the relevant publications; and (5) there were no restrictions on the year of publication of the article. In addition, in this study were excluded (1) data of hemodynamic, (2) publications of unrelated, 3), review articles 4), retracted articles, 5) the book chapters, 6) case reports, 7) the oral presentations, 8) letters to the editors of journals, 9) editorials, and 10) posters.

Process of data extraction

Two researchers examined each qualified study and then the following information extracted:

(a) name of author, publication year and country, (b) models (tissue) and duration, (c) diabetes-inducing agent (dosage) and administration route, (d) Model of animal, (e) EVs/Exo Size, (f) EVs/Exo delivery method, dose and timing, (g) Source of MSC, (h) MSCs-EVs/Exo isolation, (i) MSCs-EVs/Exo characterization and outcomes were expressed in the following categories or classifications: (a) outcomes of DM (T1D, T2D) impairment,

MSCs-EVs/Exo size & route of administration/duration of administration, and (b) MSCs-EVs/Exo administration outcomes. When $P < 0.05$ was considered significant.

Data items

We autonomously collected the information if there are of variable outcomes from each study according to the evaluation of the effectiveness of MSCs-EVs/Exo as a novel therapeutic approach for improving diabetes.

Results

Literature search and screening

An extensive search of difference electronic databases up to June 2025 obtained a total of 396 articles. After excluding duplicated articles ($n = 109$) in the first screening (according to our keywords in the title and abstract), 198 articles were discarded and 89 articles were reviewed in the second screening using our full-text criteria. Finally, 13 articles were determined to be eligible for the current investigation. The approach for doing the literature search and screening is depicted in Fig. 1.

Data extraction

The information of articles, including the name of the first author and the year of publication, model of disease (tissue) and duration, diabetes-inducing agent (dosage) and route of administration, outcomes of DM impairment, MSCs-EVs/Exo dosage, and route of administration/duration of administration, MSCs-EVs/Exo administration outcomes, was extracted and entered in Table 1 by MK, and AH confirmed the accuracy of the collected data.

Also, information from these articles about, place of study, EVs/Exo Size, model Species, EVs/Exo delivery method, dose and timing, control, MSCs source, MSCs-EVs/Exo isolation, MSCs-EVs/Exo characterization, was extracted by MK and confirmed by AH and demonstrated in Table 2.

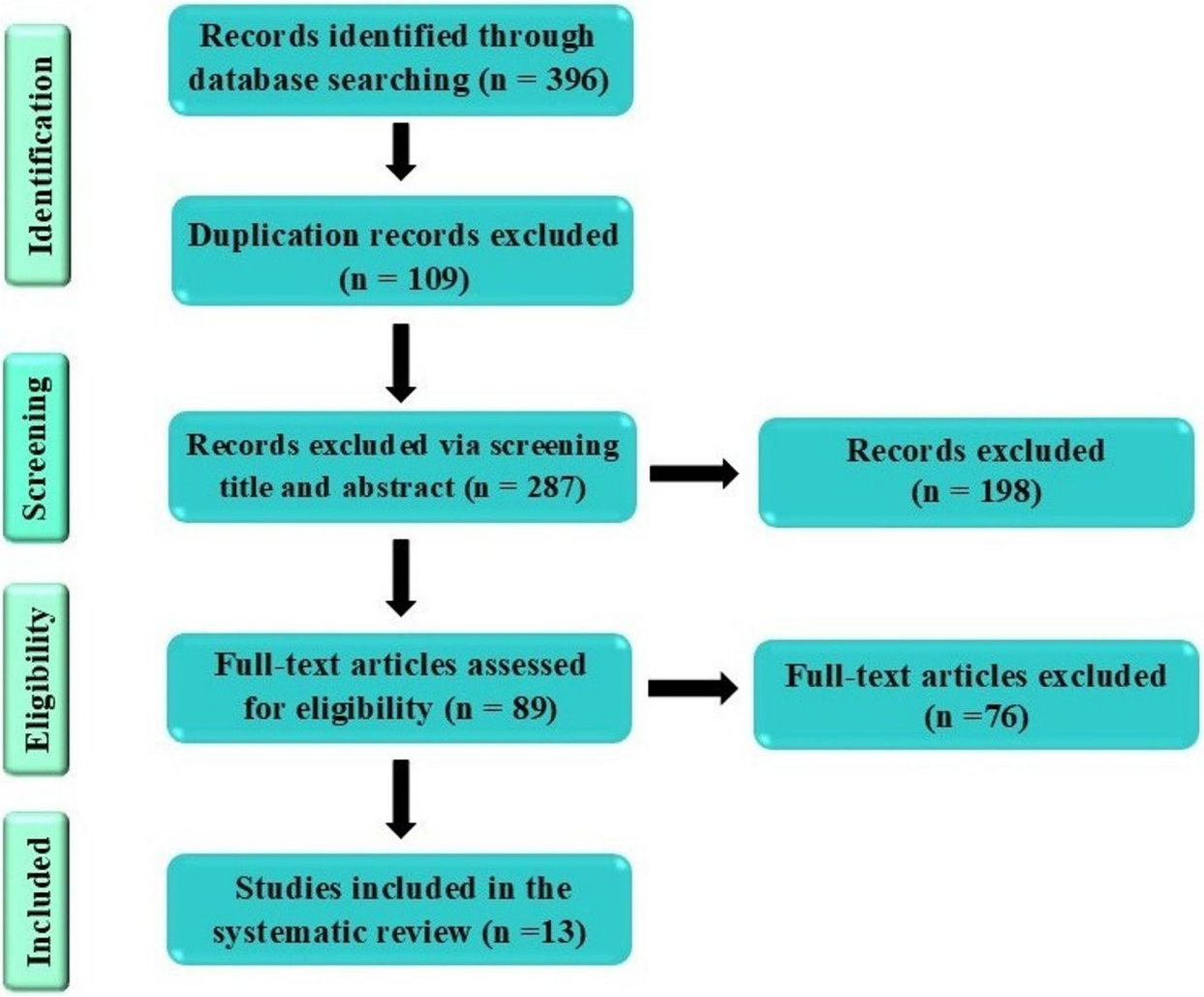


Fig. 1 PRISMA flow diagram showing the articles proses

Table 1 The characteristics of included studies

Author & Year	Model (tissue) & duration	Diabetes induced (agent dosage & route of administration)	Outcomes of T1D, T2D impairment	MSCs-derived EVs/Exo dosage & route of administration/ duration of administration	MSCs-derived EVs/Exo co-administration outcomes
Fatma Y. Meligy et al. (2025) [33]	T1D (pancreas) & 12 days	STZ (80 mg/kg) & ip	↓number of islets ↓islets' area Small islets ↓insulin positive cells ↑P62 immunoreactivity ↑expression of LC3 gene ↑FBG levels ↓acinar cell number	80 µg/ml & ip	↑number of islets ↑islets' area Large islets ↑insulin positive cells ↓P62 immunoreactivity ↓expression of LC3 gene ↓FBG levels ↑acinar cell number
Yang Ou et al. (2024) [29]	T1D (pancreas, spleen, serum) & 8 weeks	NOD/Ltf mice	↓body weight ↑blood glucose level ↓serum insulin Level ↓ levels of IL-2, IL-4 and IL-10 ↑ levels of IL-1β and IFN-γ ↑proliferation of CD4+ T lymphocyte subsets ↑proportion of Th1 cells ↓proportion of Th2 cells ↓expression of GATA-3, IL-2, IL-4, IL-10 proteins ↑expression of T-bet, IFN-γ proteins ↑expression and distribution of Fas/FasL	2 mg/kg & iv/twice a week for 8 weeks	↑body weight ↓blood glucose level ↑serum insulin Level ↑IL-2, IL-4 and IL-10 levels ↓IL-1β and IFN-γ levels, ↑proliferation of CD4+ T lymphocyte subsets ↓proportion of Th1 cells, ↑proportion of Th2 cells ↑expression of GATA-3, IL-2, IL-4, IL-10 proteins, ↓expression of T-bet, IFN-γ proteins ↓expression and distribution of Fas/FasL
Mahsa Kouhestani et al. (2023) [30]	T1D (pancreas, serum) & 2 months	STZ (55 mg/kg) & ip	↑blood glucose level ↓serum insulin level ↓body weight ↓the number of β-islets ↓the size of islets-β ↑levels of IL-1β and NF-κB ↓level of IL-10 ↓expression of insulin and Pdx1 proteins	double dose of 200 µg/µl & i.p (pancreas) by Micro-ultrasound	↓Blood glucose level ↑serum insulin level ↑body weight ↑the number of β-islets ↑the size of islets-β ↓level of IL-1β and NF-κB ↑level of IL-10 ↑expression of Insulin and Pdx1 proteins
Sara Assar Kashani et al. (2023) [26]	T1D (pancreas, serum) & 160 days	STZ (30, 35 mg/kg) & iv	↓proliferation of β-cells body weight, FBG, HbA1c, fructosamine, and C-peptide levels ↓IL-4 and IL-10 levels TGF-β1 level ↑IL-6 and IL-1β levels ↓percentage of Treg cells total volume of pancreases and volume density of β-cells	30 µg/ml & i.c (celiac artery)/two times	↑proliferation of β-cells no significant differences in body weight, FBG, HbA1c, fructosamine, and C-peptide levels ↑IL-4 and IL-10 levels no significant in TGF-β1 level ↓IL-6 and IL-1β levels ↑percentage of Treg cells no significant in total volume of pancreases and volume density of β-cells

Table 1 (continued)

Author & Year	Model (tissue) & duration	Diabetes induced (agent dosage & route of administration)	Outcomes of T1D, T2D impairment	MSCs-derived EVs/Exo dosage & route of administration/ duration of administration	MSCs-derived EVs/Exo co-administration outcomes
Rajni Sharma et al. (2021) [34]	T1D (pancreas) & 18 days	STZ (40 mg/kg) & ip	body weight ↑blood glucose levels ↓number of cells and cellular density in islets ↓proliferation of islet cells ↓level of insulin ↓expression of Reg2, Reg3, and Amy2b genes	1×10^5 MSCs-derived exosomes & iv/for 7 days total 7 times	no significant in body weight ↓blood glucose levels ↑number of cells and cellular density in islets ↑Proliferation of islet cells ↑level of insulin ↑expression of Reg2, Reg3, and Amy2b genes
Dina Sabry et al. (2020) [35]	T1D (pancreas, serum) & 4 weeks	STZ (50 mg/kg) & ip	↑levels of plasma glucose ↓serum insulin levels ↓expression of Tgfβ, Smad2 and Smad3 genes ↓expression of insulin and pdx1genes ↓expression of insulin protein ↓number of islets	200 µg/mL & ip/four doses (once per week)	↓level of plasma glucose ↑serum insulin level ↑expression of Tgfβ, Smad2 and Smad3 genes ↑expression of Insulin and pdx1genes ↑expression of insulin protein ↑number of islets
Elahe Mahdipour et al. (2019) [37]	T1D (pancreas, serum) & 6 weeks	STZ (60 mg/kg) & ip	blood glucose levels ↓serum levels of insulin ↓the β-islet number or the β-cell mass ↓the size of islets lack of insulin and pdx1 signal	10 µg/mL & tail vein	no significant differences in blood glucose ↑the serum levels of insulin ↑the β islet number or the β-cell mass ↑the size of islets presence positive of insulin and pdx1 signal
Shahrzad Nojehdehi et al. (2018) [31]	T1D (pancreas, spleen) & 2 months	STZ (50 mg/kg) & ip	↓body weight ↑blood glucose levels ↓the number of islets insulin negative in beta cells of pancreas ↓levels of IL-4, IL-10, and TGF-β ↑levels of IFN-γ and IL-17 ↓the population of Treg cells	50 µg in 1mL of PBS & ip/twice a week	↑body weight ↓blood glucose levels ↑the number of islets insulin positive in beta cells of pancreas (Anti-insulin IHC) ↑levels of IL-4, IL-10, and TGF-β ↓levels of IFN-γ and IL-17 ↑the population of Treg cells
Taeko Shigemoto-Kuroda et al. (2017) [36]	T1D (pancreas, blood) & 58 days	splenocytes from pre-diabetic NOD mice into NOD/scid mice & iv	↓plasma levels of insulin ↓number of islets in pancreas ↑insulitis in islets ↑number of CD4+ cells in islets	3 µg or 30 µg & iv	↑plasma levels of insulin ↑number of islets in pancreas ↓insulitis in islets ↓number of CD4+ cells in islets

Table 1 (continued)

Author & Year	Model (tissue) & duration	Diabetes induced (agent dosage & route of administration)	Outcomes of T1D, T2D impairment	MSCs-derived EVs/Exo dosage & route of administration/ duration of administration	MSCs-derived EVs/Exo co-administration outcomes
Jia Song et al. (2023) [32]	T2D (muscle) & 8 weeks	HFD	↓glucose tolerance and insulin tolerance ↓grip strength (muscle strength) ↓lean mass proportion ↓TA muscle mass ↓CSA of muscle fibers ↓percentage of slow in fast muscle fibers ↓number of muscle fibers ↓expression of p-AMPK and p-ULK1 ↑expression of Atrogin1 and MuRF1 proteins ↑LC3II/LC3I and p62 content ↑proportion of LC3-positive muscle fibers	200 µg & tail vein/every 3 days for 8 weeks	↑glucose tolerance and insulin tolerance ↑grip strength (muscle strength) ↑lean mass proportion ↑TA muscle mass ↑CSA of muscle fibers ↑percentage of slow in fast muscle fibers ↑number of muscle fibers ↑phosphorylation of p-AMPK and p-ULK1 ↓expression of Atrogin1 and MuRF1 proteins ↓LC3II/LC3I and p62 content ↓proportion of LC3-positive muscle fibers
Weijian Fan et al. (2023) [38]	T2D (muscle) & 28 days	DB/DB mice	blood glucose and body weight ↑permeability of vascular walls ↓fluorescence intensity of CD31 in muscle vessels ↓expression of CD105 protein ↓expression of TGF-β1 protein	100 µg in 0.1 ml PBS & tail vein	No significant differences in blood glucose and body weight ↓permeability of vascular walls ↑fluorescence intensity of CD31 in muscle vessels ↑expression of CD105 protein ↑expression of TGF-β1 protein

Table 1 (continued)

Author & Year	Model (tissue) & duration	Diabetes induced (agent dosage & route of administration)	Outcomes of T1D, T2D impairment	MSCs-derived EVs/Exo dosage & route of administration/ duration of administration	MSCs-derived EVs/Exo co-administration outcomes
Seng Kar Yap et al. (2022) [27]	T2D (pancreas, kidney, liver) & 15 days	STZ (60, 40 mg/kg) and a HFD & ip	↑blood glucose level ↓body weight ↑OGTT ↓QUICKI ↑HOMA-IR HOMA-β cells ↑serum HbA1c ↓values of RBC, Hb, MCV ↓values of WBC, neutro, lymp, mono, eosin, baso, plt values of Urea, Creat, Cl, K, Na values of TP, ALB, Glo, ALB: Glo ratio, AST, DBil, TBil ↑values of ALP and ALT	1 mg, 0.5 mg, 0.25 mg & tail vein/Every 3 days, total 5 times	↓blood glucose level ↑body weight ↓OGTT ↑QUICKI ↓HOMA-IR no significant differences in HOMA-β cells ↓serum HbA1c no significant in RBC, Hb, MCV ↑values of WBC, neutro, lymp, mono, eosin, baso, plt no significant in values of Urea, Creat, Cl, K, Na no significant in values of TP, ALB, Glo, ALB: Glo ratio, AST, DBil, TBil ↑values of ALP and ALT
YaoXiang Sun et al. (2018) [28]	T2D (muscle, liver, pancreas) & 1 month	STZ (35 mg/kg) and a 45% HFD & tail vein	↑blood glucose levels ↑OGTTs and IPITTs levels ↑HOMA-IR ↓expression of p-AKT, p(tyr)-IRS-1, p-AMPK proteins ↑level of TNF-α and IL-6 ↓expression of GLUT4, p-TBC1D4 ↓expression of p-GSK3β and GYS-2 proteins ↓expression of PK mRNA expression of GCK, CS and ICDH mRNA ↑expression of casp3 protein ↓the area and number of islet ↓level of insulin	10 mg/kg/bw in in 200 µl PBS & tail vein	↓blood glucose levels ↓OGTTs and IPITTs levels ↓HOMA-IR ↑expression of p-AKT and p(tyr)-IRS-1, p-AMPK proteins ↓level of TNF-α and IL-6 ↑expression of GLUT4, p-TBC1D4 ↑expression of p-GSK3β and GYS-2 proteins ↑expression of PK mRNA no significant in expression of CS and ICDH mRNA ↓expression of casp3 protein ↑the area and number of islet ↑level of insulin

EVs, Extracellular vesicles; Exo, Exosome; T1D, Type 1 diabetes; T2D, Type 2 diabetes; ↑, Increase; ↓, Decease; &, and; iv, Intravenous; ip, Intraperitoneal; i.c, Intera-celiac trunk artery; STZ, Streptozotocin; HFD, high-fat diet; FBG, fasting blood glucose; IL-2, Interleukin 2; IL-4, Interleukin 4; IL-6, Interleukin 6; IL-10, Interleukin 10; IL-17, Interleukin 17; IL-1β, Interleukin-1 beta; IFN-γ, Interferon gamma; TGF-β1, Transforming growth factor beta-1; NF-KB, Nuclear factor kappa B; Th1, T helper 1; Th2, T helper 2; Treg, T regulatory; FasL, Fas ligand; PDX1, Pancreatic and Duodenal homeobox 1; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin/Hemoglobin A1c; C-peptide, Connecting peptide; Reg2, Regeneration islet-derived 2; Reg3, Regeneration islet-derived 3; Amy2b, Alpha amylase 2b; TA, Tibialis anterior; CSA, Cross-sectional area; MuRF1, Muscle RING Finger 1; p-AMPK, phosphorylation AMP-activated protein kinase; p-ULK1, UNC-51-link kinase 1; LC3, Microtubule associated protein light chain 3; p62, protein 62; OGTT, Oral glucose tolerance test; IPITT, Intra-peritoneal insulin tolerant test; QUICKI, Quantitative insulin sensitivity check index; HOMA-IR, Homeostatic model assessment of insulin resistance; AKT/PKB, protein kinase B; p(tyr)-IRS-1, phosphorylation (tyrosine site) of insulin receptor substrate1; GLUT4, Glucose transporters 4; TBC1D4, TBC1 domain family member 4; GSK3β, Glycogen synthase kinase-3 beta; GYS-2, Glycogen synthase 2; PK, Pyruvate kinase; GCK, Glucokinase; CS, Citrate synthase; ICDH, Isocitrate dehydrogenase; RBC, red blood cell; Hb, haemoglobin; MCV, mean corpuscular volume; WBC, white blood cell; TP, total protein; Glo, globulin; ALB, albumin; AST, aspartate aminotransferase; DBil, direct bilirubin; TBil, total bilirubin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; Creat, creatinine; Cl, chloride; K, potassium; Na, Sodium

Table 2 Application protocols of the extracellular vesicles

Study (Location)	EVs/Exo Size	Model Species or type of animal	EVs/Exo delivery method, dose and timing	Control	MSC Source	MSCs-derived EVs/Exo Isolation	MSCs-derived EVs/Exo Characterization
Fatma Y. Meligy et al. 2025 [33]	72–79 nm	Albino rat	ip, 80 µg/rat in 0.5 ml of 0.1 m PBS,	normal, MSC	rat BM-MSCs	UC	TEM, WB
Yang Ou et al. 2024 (China) [29]	132–175 nm	mice (NOD/Ltf)	iv, 2 mg/kg in 200 µl of PBS, twice a week for 8 weeks	PBS	hUCMSCs	Ribo™ EVs Isolation Reagent	TEM, WB, NTA
Mahsa Kouhestani et al. 2023 (Iran) [30]	30–150 nm	rat	i.p, double dose of 200 µg in 100 µl of PBS	normal, MSC	hEnMSCs	UC	FESEM, DLS, WB
Sara Assar Kashani et al. 2023 (Iran) [26]	50–200 nm	rhesus monkeys	i.c, 30 µg/ml in 3 ml of PBS, two times	PBS	hBM-cMSC	UC and sucrose density gradient	TEM, SEM, DLS, WB
Rajni Sharma et al. 2021 (India) [34]	50–140 nm	mice (C57BL/6)	iv, 1×10^5 MSCs-derived Exo/mice, for 7 days	PBS	UCMSCs	UC	SEM, DLS, WB
Dina Sabry et al. 2020 (Egypt) [35]	100 nm	rat (albino)	ip, four doses of 200 µg/mL, for 4 weeks	normal, MSC	rat BM-MSCs	UC	TEM
Elahe Mahdipour et al. 2019 (Iran) [37]	30–150 nm	rat	tail vein, 10 µg in PBS,	PBS	hMenSCs	UC	FESEM, AFM, WB
Shahrzad Nojehdehi et al. 2018 (Iran) [31]	40–100 nm	mice (C57BL/6)	ip, 50 µg in 1mL of PBS, for 4 weeks (twice a week)	normal	mice AD-MSCs	UC	TEM, SEM, DLS
Taeko Shigemoto-Kuroda et al. 2017 (USA) [36]	100 nm	mice (NOD/scid)	iv, 3 µg or 30 µg	PBS	HMSCs	the column resin and UC	SEM, NTA, WB
Jia Song et al. 2023 (China) [32]	130 nm	mice (db/db)	tail vein, 200 µg in 200 µL PBS, every 3 days for 8 weeks	PBS	hUCMSCs	UC	TEM, WB, NTA
Weijian Fan et al. 2023 (China) [38]	30–200 nm	mice (DB/DB)	tail vein, 100 µg in 0.1 ml PBS	PBS	hUCMSCs	UC	TEM, NTA, WB
Seng Kar Yap et al. 2022 (Malaysia) [27]	97 nm (less than 220 nm)	rat	tail vein, 1 mg, 0.5 mg, 0.25 mg, Every 3 days, total 5 times	PBS	hUCMSCs	Millipore™ Centricon® Plus70 Centrifugal Filter	TEM, NTA, WB
YaoXiang Sun et al. 2018 (China) [28]	30–150 nm	rat	tail vein, 10 mg/kg/bw in 200 µl PBS, every 3 days for 5 cycles	PBS	hUCMSCs	NR	TEM, NTA, WB

HUCMSCs, human umbilical cord Mesenchymal stem cells; hEnMSCs, human Endometrial Mesenchymal stem cells; BM-MSCs, Bone marrow Mesenchymal stem cells; hMenSCs, human Menstrual stem cells; AD-MSCs, Adipose-derived Mesenchymal stem cells; PBS, Phosphate buffer saline; TEM, Transmission electron microscope; SEM, Scanning electron microscope; FESEM, Field emission scanning electron microscopy; AFM, Atomic force microscopy; NTA, Nanoparticle tracking analysis; DLS, Dynamic light scatting; WB, Western blot; UC, Ultracentrifuge; NR, not reported

The role of MSCs-derived-EVs/Exo against biochemical, molecular and histological changes induced by diabetes mellitus (T1D, T2D)

Biochemical changes

In the current study, the changes of biochemical are indicators for identifying disorders produced by DM (T1D, T2D). According to the results of this study, DM induces a significant increase in blood glucose level, serum HbA1c, C-peptide levels as hyperglycemia situation and OGTT and IPITTs levels, HOMA-IR levels as glucose tolerance and insulin resistance status [26–28], and also IL-1β, IL-6, IFN-γ, NF-κB, TNF-α, IL-17 levels and proliferation of CD4 + T lymphocyte as immune-inflammation system mediators compared to control group animals. Meanwhile, MSCs-derived EVs/Exo improved hyperglycemia condition and inflammatory responses and reduced insulin sensitivity compared to the diabetic groups [26, 29, 30].

The results of this study showed that DM considerably reduced body weight, serum insulin and IL-2, IL-4, IL-10, TGF-β levels as anti-inflammatory cytokine compared to normal group. These immune-inflammatory markers were restored with MSCs-EVs/Exo administration to normal levels [29–31].

Molecular changes

The changes of molecular are markers for identifying damages of the cellular created by DM (T1D, T2D). Based on the results of current study, DM induces a significant elevation in expression of T-bet and IFN-γ proteins as inflammation mediators, casp3 protein, the ratio of LC3II/LC3I and p62 content compared to the healthy animals group. MSCs-EVs/Exo decreased the expression of T-bet, IFN-γ, casp3, LC3I, LC3II and p62 proteins compared to diabetic animals group [29, 32, 33].

The present study results indicated that DM dramatically diminished the expression of insulin, pdx1, Atrogin1, MuRF1, GATA-3, IL-2, IL-4, IL-10, p-AMPK, p-ULK1, p-AKT, p(tyr)-IRS-1, CD105, TGF-β1, GLUT4, p-TBC1D4, p-GSK3β and GYS-2 proteins and expression of TGF-β, Smad2, Smad3, Reg2, Reg3, Amy2b and PK genes as mediators and regulators of different signaling pathways compared to the healthy group. This is while, administration of MSCs-derived EVs/Exo restored these molecular changes to natural levels [29, 34, 35].

Histological changes

The changes of histological are signs for identifying damages of tissue induced by DM (T1D, T2D). The study findings show that DM induced an increase in insulitis and number of CD4 + cells in islets, p62 positive cells, permeability of vascular walls, proportion of LC3-positive muscle fibers, expression and distribution of Fas/FasL compared to the standard group. However, treatment with MSCs-derived EVs/Exo reversed back these changes of histological to normal [29, 32, 36].

In addition, results of this research demonstrated that DM decreased the number, mass and size of β-islet, insulin immunoreactivity and cellular density in β-cells, proliferation of islet cells, lack of insulin and pdx1 signal in beta cells of pancreas, an ill-defined ghost of endocrine cells with highly vacuolated cytoplasm, also cells-β with hyperchromatic nuclei and irregular nuclear envelope, acinar cells, acinar cells have zymogen granules of variable size, a small heterochromatin nucleus with indistinct nucleolus and irregular arrangement of the rough endoplasmic reticulum, fluorescence intensity of CD31 in muscle vessels, CSA of muscle fibers, percentage of slow in fast muscle fibers and number of muscle fibers compared to the normal group animals. While, in the groups treated with MSCs-derived EVs/Exo, these changes were reversed to their normal state. Also, total volume of pancreases and volume density of β-cells no significant differences in the experimental groups [30, 33, 34, 37, 38].

Study of clinical trial

Although, in some animal studies have used MSCs-derived EVs/Exo for the treatment of diabetes, only one clinical study has been reported in the clinicaltrial.gov database, that has investigated the therapeutic effects of EVs (MV) in type 1 diabetes patients. In this trial clinical (NCT02138331) which was recorded by Sahel Teaching Hospital (Egypt), the effect of administering umbilical cord blood-derived EVs (Microvesicles) on β-cell Mass and glycemic control in T1D Patients investigated. This patient received double dose of MV for Three months.

Reasons like reporting of incomplete results in animal studies, lake of GMP principles and standards for EVs isolation, purification, and quantification, also our limited information and understanding of the safety, efficacy and pharmacokinetic data of exosomes could indicate the registration of a limited number of trial clinical. So, it is necessary to create a standard protocol for the evaluation of diabetic patient's outcomes treated with exosomes and expansion of MSCs for preparation and production of EVs/Exo in a large-scale.

Discussion

The aim of this study was to investigate the detrimental impacts of diabetes on different organs specially pancreas. In addition, researchers examined the therapeutic effect of MSCs-derived EVs/Exo on these adverse outcomes. It should be noted that, according to knowledge and our research in different database, this study is the first systematic review on the therapeutic efficacy of MSCs-derived EVs/Exo on pre-clinical and clinical studies of diabetes (T1D, T2D). The following points further highlight the novel contribution and unique position of our work. Previous meta-analyses and systematic reviews have focused exclusively on the role of EVs/Exo in the management of diabetic complications, such as wound healing, nephropathy, or cardiomyopathy. In contrast, our study is the first to specifically focus on the efficacy of EVs/Exo in modulating the core pathophysiology of type 1 and type 2 diabetes, including glycemic control, beta-cell regeneration/repair, regulation of inflammatory-immune responses, and insulin sensitivity. Furthermore, we applied strict inclusion criteria and selected only studies that used MSCs-derived EVs/Exo (from different sources) and specifically addressed T1D or T2D. Table 1 shows summary of the data about the effects of DM alone or in treatment with MSCs-derived EVs/Exo on β-islet cells/pancreas and muscle tissues. In addition, a summary of the characteristics of used MSCs-derived EVs/Exo in the included studies were listed in Table 2. Also, a schematic of significant changes in beta cells with

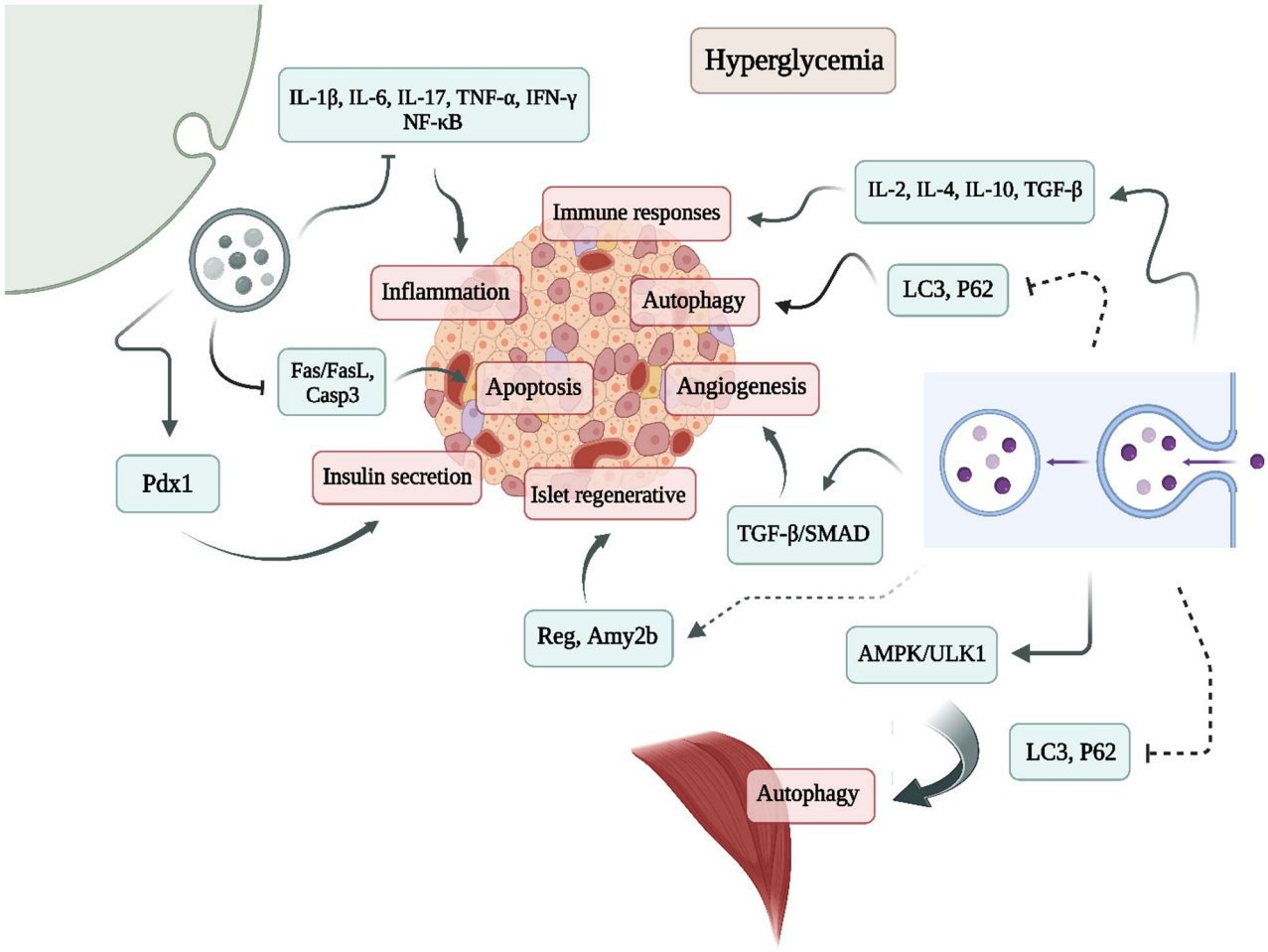


Fig. 2 The diverse mechanisms involved in diabetes mellitus. Schematic diagram of the protective function of MSCs-derived EVs/Exo against diabetes by improving tissue damages caused by severe hyperglycemia condition. MSCs-derived EVs/Exo inhibits immune and inflammatory reactions, apoptosis, oxidative stress and as well as up regulates the expression of important functional proteins, as a result, prevents the progression of diabetes and leads to reduction in destructive pathologies

severe hyperglycemic conditions and the effective effects of MSCs-derived EVs/Exo administration on these alterations are depicted in Fig. 2.

DM includes a range of metabolic and autoimmune disorders and generally occurs in people with a genetic background, which due to a severe defect in insulin secretion or insulin inefficiency leads to chronic hyperglycemia and also changes in the metabolism of other metabolites [39, 40]. According IDF, the majority of countries spend 5% to 25% of their health expenses on this disease. Also, this organization has estimated that the total health care costs related to diabetes reached more than 850 billion dollars in 2017 [41]. Although the cause of diabetes has not been fully determined, it is believed that the pathogenesis of this disease is related to many factors. It is believed that the pathogenesis of diabetes is related to a complex interaction between genetic and environmental factors. However, the initial initiating events of this disease are still unknown [42]. Generally, hyperglycemia by activating several cell death signaling pathways, including apoptosis, necrosis and autophagy, as well as by activating inflammatory and immune pathways in beta cells, leads to the reduction and loss of the mass of insulin-producing beta cells and the progression of diabetes [43, 44].

Activation of immune and inflammatory pathways is initiated by the infiltration of dendritic cells and macrophages (APCs) into the pancreatic islets, which leads to the migration of B cells and TCD4 + and TCD8 + cells from the pancreatic lymph nodes into the pancreatic islets, ultimately leading to beta-islet inflammation, beta-cell destruction, and the progression of diabetes. TCD4 + and TCD8 + cells also produce proinflammatory cytokines such as perforin, interferon gamma (IFN¥), TNF-α, IL-6, and IL-1β, which lead to beta cell apoptosis [19, 44, 45]. IL-1β inhibits the normal physiological function of pancreatic beta cells, and TNF-α and IFN-γ synergistically enhance the cytotoxicity of IL-1β [46, 47]. NF-kB

is also a key transcription factor that plays an important regulatory role in many pathophysiological processes, including inflammatory processes, immune responses, as well as cell survival and death. So, various studies have identified the role of NF-kB signaling as an important inflammatory pathway that controls chronic inflammation in many inflammatory diseases [48, 49]. On the other hand, factors such as IL-2, IL-4, and IL-10 are pleiotropic anti-inflammatory cytokines and are known as key and primary regulators of immunity and mainly suppress important inflammatory and immune responses, thereby preventing the progression of various inflammatory and autoimmune lesions [50, 51]. The studies included in this systematic review confirmed the activation of immune and inflammatory pathways in T1D and T2D. The results of these studies showed an increase in the levels of IFN¥, TNF-α, IL-6, IL-1β and NF-kB, and also a decrease in anti-inflammatory cytokines levels includes, IL-2, IL-4 and IL-10. Meanwhile, MSCs-derived EVs/Exo could restore these immune and inflammatory factors [26, 28–31]. Various studies, in support of our study, have shown that MSCs-derived exosomes have potent anti-inflammatory and immunomodulatory properties that are highly effective in regenerating damaged beta cells and reactivating them to produce and secrete insulin, leading to improvement in diabetes [35, 52, 53].

CD4 + T-helper (Th) lymphocytes are a functionally heterogeneous cell population, consisting of at least three subsets, Th1, Th2, and Th0, characterized by their cytokine production profiles. Th1 cells are involved in the pathogenesis of diabetes by producing inflammatory cytokines, while Th2 cells, with their anti-inflammatory and modulatory activity, could be useful for the prevention and treatment of diabetes. Therefore, impaired differentiation of Th0 cells into Th1/Th2 cells could contribute to the development of diabetes [54, 55]. This differentiation is influenced by two transcription factors, GATA-3 and T bet (T-box). T-bet induces the Th1 subset, whereas the transcription factor GATA-3 is responsible for the differentiation and effective responses of Th2 cells. Therefore, controlling the expression of T-bet/GATA-3 could be very useful in the prevention and understanding of the pathology of diabetes [56, 57]. The documentation of this study showed that MSCs-derived EVs/Exo-based therapy in diabetic animals affects the control of Tbet/GATA-3 expression, leading to an increase in Th2 cells and a decrease in Th1, which consequently controls the secretion of various inflammatory and immune factors, ultimately leading to the inhibition of beta-cell destruction and diabetes [29].

Regulatory T cells (Tregs) are a heterogeneous population of lymphocytes that help to resolve tissue inflammation by suppressing autoreactive T cells and regulating immune responses. Tregs play a key role in establishing and maintaining immune tolerance, such that defects in the number and function of these cells may be underlying causes of many autoimmune disorders, including T1D [58, 59]. The results of this study showed that treatment of T1D mice with MSCs-derived exosomes significantly increased the Treg cell population [31].

Transforming growth factor beta (TGF-β) is a pleiotropic signaling pathway whose function is achieved through a combination of receptors and ligands such as SMAD transcription factors and is involved in numerous processes such as cell growth, differentiation, and apoptosis [60, 61],. CD105 is a lateral transmembrane glycoprotein and is expressed on activated vascular endothelial cells. In general, TGF-β1 activates the Smad1/5/8 signaling pathway through CD105 and promotes endothelial cell migration, proliferation, and tube formation [62, 63]. MSCs-derived-Exo possibly by enhancing angiogenesis and directly stimulating endothelial cell proliferation through TGF-β1 and the CD105/TβR-II complex can be repair endothelial cell damage and improve vascular permeability [64]. The results of this study showed a decrease in the expression of T-GFβ, SMAD2, SMAD3, and CD105 proteins, which were increased by MSCs-derived exosomes treatment [26, 31, 35, 38].

In diabetic patients, accompanied by severe inflammation, beta islets undergo apoptosis and death, which is likely one of the main mechanisms of beta cell death. Increased expression and distribution of Fas/FasL on the cell surface acts as a death receptor by activating the caspase-3 protein, leading to the initiation of the apoptotic cell death pathway [65, 66]. Some documents, in support of our study have shown that the expression of Fas receptor and caspase-3 protein is increased in diabetic groups and by stimulating the Fas/FasL/apoptosis signaling pathway, it causes destruction and death of beta islets, while a significant decrease in the expression of these factors is observed in groups treated with MSCs-EVs/Exo [28, 29, 67, 68]. Thus as expected, in the H&E-stained tissue sections from MSCs-EVs/Exo -treated animals observed larger islets with greater numbers and normal morphology compared to the extensive destruction and loss of β-islets in diabetic groups [30, 37].

Reg family proteins with anti-apoptotic and anti-inflammatory properties are known as regenerative proteins of the islets of Langerhans [69, 70]. AMY2B (alpha amylase 2B) is also mainly associated with the pathways of glucose metabolism and digestion of dietary glycogen [71, 72]. The findings of this study showed that treatment with MSCs-EVs/Exo in diabetic mice by increasing the expression of Reg family and AMY2B genes actived the ability to produce beta islets and improved insulin levels [34].

Insulin is a peptide hormone secreted by pancreatic islets that is essential for maintaining glucose

homeostasis and regulating metabolism [73, 74]. Pdx1 is not only known as a master regulator of pancreatic growth and survival, but also a key factor that controls most of the vital functions of beta cells, including insulin biosynthesis and sensitivity to apoptosis, and its decreased expression leads to beta cell apoptosis and decreased insulin production and secretion [75–77]. The findings of this study showed that the MSCs-EVs/Exo-treated groups showed a significant increase in pdx1 protein expression as well as insulin, which led to increased pancreatic islets survival and improvement of diabetes [30, 35, 37].

HbA1C, or glycosylated hemoglobin, indicates the patient's average blood sugar over the past two to three months, and there is a direct relationship between HbA1C and complications of diabetes [78–80]. C-peptide connects the alpha and beta chains of proinsulin, and there is a direct relationship between insulin deficiency and C-peptide deficiency in diabetes [81–83]. The findings from this study showed that MSCs-EVs/Exo treatment improved hyperglycemia in diabetic animals by reducing HbA1C and increasing C-peptide levels [26, 27]. Weight gain was also observed in treated animals compared to diabetic animals that experienced severe weight loss and polyuria [29–31, 34, 37]. Furthermore, evaluation of homeostasis model assessment of insulin resistance (HOMA-IR), oral glucose tolerance (OGTT), and intraperitoneal insulin tolerance (IPITTs) in MSCs-EVs/Exo-treated groups showed significant improvements in these indices [27].

Autophagy is a regulated self-destructive process and is closely linked to inflammation and oxidative stress, which may play a role in the pathogenesis of diabetes [46, 84]. AMPK and ULK1 proteins are effective in activating autophagy [85, 86]. p62 is an autophagy receptor that acts as a marker for the clearance of protein aggregates, toxic cellular debris, and inhibition of autophagy. LC3 is a specific marker for autophagy activation and autophagosome formation [87, 88]. The autophagy process is critical for controlling skeletal muscle function and maintaining muscle mass homeostasis. Studies have shown that in obese diabetic mice, along with reduced expression of AMPK/ULK1 proteins, accumulation of LC3 and p62 markers in skeletal muscles and inhibition of autophagy are evident, which ultimately leads to severe muscle weakness and atrophy in diabetic animals. Studies have shown that MSCs-extracted-EVs/Exo can improve skeletal atrophy and frailty by activating autophagy through the AMPK/ULK1 pathway in diabetic animals [86, 89]. On the other hand, excessive and inappropriate autophagy activity may damage cells. Therefore, the exacerbation of autophagy can cause beta cell death and diabetes. The results of this study showed that MSCs-derived-EVs/Exo can prevent beta cell death and be effective in improving diabetes by significantly reducing the expression of LC3 and P62 [28, 32, 33].

It should be noted that in the articles included in this study, ultracentrifugation was used as the gold standard method for the isolation and preparation of EVs. Therefore, heterogeneity in EVs preparation is significantly reduced, thereby limiting its potential impact on the comparison of results.

Generally, this systematic study found that MSCs-derived EVs/Exo have anti diabetic effects and protective potential, including immunomodulatory, anti-apoptotic, and antioxidant properties. These amazing and interesting properties are achieved by influencing various mediators such as IL-1β, IL-6, I L-17, IL-2, IL-4, IL-10, IFN-γ, NF-κB, TNF-α, TGF-β and the expression of proteins caspase3, LC3I/II, p62, p-AMPK, p-ULK1, p-AKT, Smad and Reg. As a result, MSCs-derived EVs/Exo help in reducing the histopathological damages that diabetes causes to pancreas and muscle. It is worth noting that these findings are derived from non-clinical studies and one clinical study. To gain a complete and comprehensive understanding of this disease, further clinical studies in diabetic people and investigation of other relevant pathways in this disease are needed.

Conclusion

Main Finding: MSCs-derived EVs/Exo can be considered as a promising source for repairing damaged tissues with safe and cost-effective therapeutic potential. Therefore, we suggest that administering MSCs-derived EVs/Exo could be a novel and powerful therapeutic strategy for diabetic patients who have poor response to conventional treatments.

Limitation/Gap and Future Directions: It should be noted that, only one clinical trial was included in this systematic. This means that, we were faced with a serious shortage of human data. Therefore, to achieve better results and transfer this treatment method to the clinic, it is necessary to evaluate the safety, efficacy and feasibility of this therapeutic approach in humans.

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The authors declare that they have not use AI-generated work in this manuscript.

Author contributions
Mahsa Kouhestani: Conceptualization; Data curation; Methodology; Roles/Writing—original draft. Asieh Hosseini: Conceptualization; Investigation; Methodology; Supervision Roles; review and editing.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consnent to participate
The ethical committee of Iran University of Medical Sciences approved this systematic review (IR.IUMS.REC.1403 – 423).

Consent for publication
All authors give consent for publication.

Competing interests
The authors declare no competing interests.

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References

1. Hass R, et al. Different populations and sources of human mesenchymal stem cells (MSC): a comparison of adult and neonatal tissue-derived MSC. Cell Commun Signal. 2011;9:1–14.
2. Newton WC, et al. Stem cell-derived exosomes: a novel vector for tissue repair and diabetic therapy. J Mol Endocrinol. 2017;59(4):R155–65.
3. Cho J, et al. A review of clinical trials: mesenchymal stem cell transplant therapy in type 1 and type 2 diabetes mellitus. Am J Stem Cells. 2018;7(4):82.
4. Zhao R, et al. Drug delivery system in the treatment of diabetes mellitus. Front Bioeng Biotechnol. 2020;8:880.
5. Khatri R, Petry SF, Linn T. Intrapancreatic MSC transplantation facilitates pancreatic islet regeneration. Stem Cell Res Ther. 2021;12:1–14.
6. Saha S, Al-Rifai RH, Saha S. Diabetes prevalence and mortality in COVID-19 patients: a systematic review, meta-analysis, and meta-regression. J Diabetes Metab Disord. 2021;20:939–50.
7. Gurunathan S, Kang MH, Kim J-H. Diverse effects of exosomes on COVID-19: a perspective of progress from transmission to therapeutic developments. Front Immunol. 2021;12:716407.
8. Rekittke NE, et al. Regenerative therapy of type 1 diabetes mellitus: from pancreatic islet transplantation to mesenchymal stem cells. Stem Cells Int. 2016;2016(1):3764681.
9. Rackham C, et al. Co-transplantation of mesenchymal stem cells maintains islet organisation and morphology in mice. Diabetologia. 2011;54:1127–35.
10. Triolo TM, Bellin MD. Lessons from human islet transplantation inform stem cell-based approaches in the treatment of diabetes. Front Endocrinol. 2021;12:636824.
11. Chen S, Du K, Zou C. Current progress in stem cell therapy for type 1 diabetes mellitus. Stem Cell Res Ther. 2020;11(1):275.
12. Scuteri A, Monfrini M. Mesenchymal stem cells as new therapeutic approach for diabetes and pancreatic disorders. Int J Mol Sci. 2018;19(9):2783.
13. Lee B-C, Kang I, Yu K-R. Therapeutic features and updated clinical trials of mesenchymal stem cell (MSC)-derived exosomes. J Clin Med. 2021;10(4):711.
14. Moghadasi S, et al. A paradigm shift in cell-free approach: the emerging role of MSCs-derived exosomes in regenerative medicine. J Transl Med. 2021;19:1–21.
15. Corrêa RR, et al. Extracellular vesicles as a therapeutic tool for kidney disease: current advances and perspectives. Int J Mol Sci. 2021;22(11):5787.
16. Esfandyari S, et al. Exosomes as biomarkers for female reproductive diseases diagnosis and therapy. Int J Mol Sci. 2021;22(4):2165.
17. Huda MN, et al. Potential use of exosomes as diagnostic biomarkers and in targeted drug delivery: progress in clinical and preclinical applications. ACS Biomater Sci Eng. 2021;7(6):2106–49.
18. Kourembanas S. Exosomes: vehicles of intercellular signaling, biomarkers, and vectors of cell therapy. Annu Rev Physiol. 2015;77(1):13–27.
19. Delmastro MM, Piganelli JD. Oxidative stress and redox modulation potential in type 1 diabetes. J Immunol Res. 2011;2011(1):593863.
20. Xie Z, Chang C, Zhou Z. Molecular mechanisms in autoimmune type 1 diabetes: a critical review. Clin Rev Allergy Immunol. 2014;47:174–92.
21. Warshauer JT, Bluestone JA, Anderson MS. New frontiers in the treatment of type 1 diabetes. Cell Metab. 2020;31(1):46–61.
22. Knip M, Siljander H. Autoimmune mechanisms in type 1 diabetes. Autoimmun Rev. 2008;7(7):550–7.
23. Zhang B, et al. Mesenchymal stromal cell exosome–enhanced regulatory T-cell production through an antigen-presenting cell–mediated pathway. Cytotherapy. 2018;20(5):687–96.
24. Mazini L, Rochette L, Malka G. Exosomes contribution in COVID-19 patients' treatment. J Transl Med. 2021;19:1–8.
25. Xiong J, et al. Mesenchymal stem cell exosomes as a new strategy for the treatment of diabetes complications. Front Endocrinol. 2021;12:646233.
26. Kashani SA, et al. Immunomodulatory potential of human clonal mesenchymal stem cells and their extracellular vesicle subpopulations in an inflammatory-mediated diabetic rhesus monkey model. Life Sci. 2023;329:121950.
27. Yap SK, et al. Human umbilical cord mesenchymal stem cell-derived small extracellular vesicles ameliorated insulin resistance in type 2 diabetes mellitus rats. Pharmaceutics. 2022;14(3):649.
28. Sun Y, et al. Human mesenchymal stem cell derived exosomes alleviate type 2 diabetes mellitus by reversing peripheral insulin resistance and relieving β-cell destruction. ACS Nano. 2018;12(8):7613–28.
29. Ou Y, et al. Effects of extracellular vesicles derived from human umbilical cord blood mesenchymal stem cells on cell immunity in Nonobese mice. Stem Cells Int. 2024;2024(1):4775285.
30. Kouhestani M, et al. Study of anti-inflammatory and immunomodulatory potential of endometrial mesenchymal stem cells-derived exosomes with micro-ultrasound (μUS) guidance in regeneration β-islets on T1D animal model. J Drug Deliv Sci Technol. 2023;86:104666.
31. Nojehdehi S, et al. Immunomodulatory effects of mesenchymal stem cell–derived exosomes on experimental type-1 autoimmune diabetes. J Cell Biochem. 2018;119(11):9433–43.
32. Song J, et al. Mesenchymal stromal cells ameliorate diabetes-induced muscle atrophy through exosomes by enhancing AMPK/ULK1-mediated autophagy. J Cachexia Sarcopenia Muscle. 2023;14(2):915–29.
33. Meligy FY, et al. Mesenchymal stem cells versus mesenchymal stem cells-derived exosomes as potential autophagy pathway modulators in a diabetic model. Adv Med Sci. 2025. https://doi.org/10.1016/j.advms.2025.02.004.
34. Sharma R, et al. Exosomes secreted by umbilical cord blood-derived mesenchymal stem cell attenuate diabetes in mice. J Diabetes Res. 2021;2021(1):9534574.
35. Sabry D, et al. The effect of exosomes derived from mesenchymal stem cells in the treatment of induced type 1 diabetes mellitus in rats. Biotechnol Lett. 2020;42:1597–610.
36. Shigemoto-Kuroda T, et al. MSC-derived extracellular vesicles attenuate immune responses in two autoimmune murine models: type 1 diabetes and uveoretinitis. Stem Cell Reports. 2017;8(5):1214–25.
37. Mahdipour E, Salmasi Z, Sabeti N. Potential of stem cell-derived exosomes to regenerate β islets through Pdx-1 dependent mechanism in a rat model of type 1 diabetes. J Cell Physiol. 2019;234(11):20310–21.
38. Fan W, et al. Human umbilical cord mesenchymal stem cell-derived exosomes promote microcirculation in aged diabetic mice by TGF-β1 signaling pathway. Diabetol Metab Syndr. 2023;15(1):234.
39. Zhu Y, et al. Impaired bone regenerative effect of exosomes derived from bone marrow mesenchymal stem cells in type 1 diabetes. Stem Cells Transl Med. 2019;8(6):593–605.
40. Szot GL, et al. Tolerance induction and reversal of diabetes in mice transplanted with human embryonic stem cell-derived pancreatic endoderm. Cell Stem Cell. 2015;16(2):148–57.
41. Dang LT-T, Phan NK, Truong KD. Mesenchymal stem cells for diabetes mellitus treatment: new advances. Biomed Res Ther. 2017;4(1):1062–81.
42. Paschou SA, et al. On type 1 diabetes mellitus pathogenesis. Endocr Connect. 2018;7(1):R38–46.
43. Li X, et al. Effects of hyperglycemia and diabetes mellitus on coagulation and hemostasis. J Clin Med. 2021;10(11):2419.
44. Ohiagu FO, Chikezie PC, Chikezie CM. Pathophysiology of diabetes mellitus complications: metabolic events and control. Biomed Res Ther. 2021;8(3):4243–57.
45. Roep BO. The role of T-cells in the pathogenesis of type 1 diabetes: from cause to cure. Diabetologia. 2003;46:305–21.
46. Demirtas L, et al. Apoptosis, autophagy & endoplasmic reticulum stress in diabetes mellitus. Indian J Med Res. 2016;144(4):515–24.
47. Tsalamandris S, et al. The role of inflammation in diabetes: current concepts and future perspectives. Eur Cardiol Rev. 2019;14(1):50.

48. Suryavanshi S, Kulkarni Y. NF-κβ: a potential target in the management of vascular complications of diabetes. Front Pharmacol. 2017;8:798.
49. Capece D, et al. NF-κB: blending metabolism, immunity, and inflammation. Trends Immunol. 2022;43(9):757–75.
50. Lu J, et al. Cytokines in type 1 diabetes: mechanisms of action and immunotherapeutic targets. Clin Transl Immunol. 2020;9(3):e1122.
51. Pfeiffer SE, et al. Effect of IL4 and IL10 on a human in vitro type 1 diabetes model. Clin Immunol. 2022;241:109076.
52. Baharlooi H, et al. Mesenchymal stem cell-derived exosomes: a promising therapeutic Ace card to address autoimmune diseases. Int J Stem Cells. 2020;13(1):13–23.
53. Lai P, et al. Novel insights into MSC-EVs therapy for immune diseases. Biomark Res. 2019;7:1–10.
54. Soltani S, et al. Extracellular vesicle therapy for type 1 diabetes. Front Immunol. 2022;13:865782.
55. Mahlangu T, et al. A systematic review on the functional role of Th1/Th2 cytokines in type 2 diabetes and related metabolic complications. Cytokine. 2020;126:154892.
56. Fang D, Healy A, Zhu J. Differential regulation of lineage-determining transcription factor expression in innate lymphoid cell and adaptive T helper cell subsets. Front Immunol. 2023;13:1081153.
57. Wali JA, Thomas HE, Sutherland AP. Linking obesity with type 2 diabetes: the role of T-bet. Diabetes Metab Syndr Obes Targets Ther. 2014. https://doi.org/10.2147/DMSO.S51432.
58. Kornete M, Mason ES, Piccirillo CA. Immune regulation in T1D and T2D: prospective role of Foxp3 + Treg cells in disease pathogenesis and treatment. Front Endocrinol. 2013;4:76.
59. Grinberg-Bleyer Y, et al. Pathogenic T cells have a paradoxical protective effect in murine autoimmune diabetes by boosting Tregs. J Clin Invest. 2010;120(12):4558–68.
60. Hata A, Chen Y-G. TGF-β signaling from receptors to Smads. Cold Spring Harb Perspect Biol. 2016;8(9):a022061.
61. Wang L, et al. TGF-beta as a master regulator of diabetic nephropathy. Int J Mol Sci. 2021;22(15):7881.
62. Deng Z, et al. TGF-β signaling in health, disease and therapeutics. Signal Transduct Target Ther. 2024;9(1):61.
63. Browne S, et al. TGF-β1/CD105 signaling controls vascular network formation within growth factor sequestering hyaluronic acid hydrogels. PLoS One. 2018;13(3):e0194679.
64. AbuBakr N, et al. Functional and histological evaluation of bone marrow stem cell-derived exosomes therapy on the submandibular salivary gland of diabetic Albino rats through TGFβ/Smad3 signaling pathway. Heliyon. 2020. https://doi.org/10.1016/j.heliyon.2020.e03789.
65. Yamada A, et al. Dual role of Fas/FasL-mediated signal in peripheral immune tolerance. Front Immunol. 2017;8:403.
66. Wang M, Su P. The role of the Fas/FasL signaling pathway in environmental toxicant-induced testicular cell apoptosis: an update. Syst Biol Reprod Med. 2018;64(2):93–102.
67. Zhu J, et al. Emerging role of extracellular vesicles in diabetic retinopathy. Theranostics. 2024;14(4):1631.
68. Chen F, et al. Adipose-derived stem cell-derived exosomes ameliorate erectile dysfunction in a rat model of type 2 diabetes. J Sex Med. 2017;14(9):1084–94.
69. He Z. The role of reg proteins in pancreatic regeneration. J Mol Biomarkers Diagn. 2016;7:1–4.
70. Uppal SS, et al. Expression of REG Iα gene in type 2 diabetics in Pakistan. Diabetol Metab Syndr. 2015;7:1–7.
71. Kalinovskii AP, et al. Natural inhibitors of mammalian α-amylases as promising drugs for the treatment of metabolic diseases. Int J Mol Sci. 2023;24(22):16514.
72. Abdulkareem MA, et al. Genetic factors and the role of pancreatic amylase in the pathogenesis of type 2 diabetes. Egypt J Med Hum Genet. 2024;25(1):33.
73. Rahman MS, et al. Role of insulin in health and disease: an update. Int J Mol Sci. 2021;22(12):6403.
74. Karas JA, Wade JD, Hossain MA. The chemical synthesis of insulin: an enduring challenge. Chem Rev. 2021;121(8):4531–60.
75. Memon B, et al. PDX1–/NKX6. 1 + progenitors derived from human pluripotent stem cells as a novel source of insulin-secreting cells. Diabetes Metab Res Rev. 2021;37(5):e3400.
76. Aftab N, Arshad H. Overexpression of PDX1 and NKX6. 1 as a treatment for type 1 diabetes: a research protocol. Undergrad Res Nat Clin Sci Technol J. 2021;5:1–11.
77. Al-Adsani AM, et al. Expression profiling of Pdx1, Ngn3, and MafA in the liver and pancreas of recovering streptozotocin-induced diabetic rats. Genes. 2022;13(9):1625.
78. Agiostratidou G, et al. Standardizing clinically meaningful outcome measures beyond HbA1c for type 1 diabetes: a consensus report of the American association of clinical endocrinologists, the American association of diabetes educators, the American diabetes association, the endocrine Society, JDRF international, the Leona M. and Harry B. Helmsley charitable Trust, the pediatric endocrine Society, and the T1D exchange. Diabetes Care. 2017;40(12):1622–30.
79. Gebel E. The start of something good: the discovery of HbA1c and the American diabetes association Samuel Rahbar outstanding discovery award. Diabetes Care. 2012;35(12):2429.
80. Yuan Y, et al. The association between self-monitoring of blood glucose and HbA1c in type 2 diabetes. Front Endocrinol. 2023;14:1056828.
81. Wahren J, Larsson C. C-peptide: new findings and therapeutic possibilities. Diabetes Res Clin Pract. 2015;107(3):309–19.
82. Jones A, Hattersley A. The clinical utility of C-peptide measurement in the care of patients with diabetes. Diabet Med. 2013;30(7):803–17.
83. Lachin JM, et al. Impact of C-peptide preservation on metabolic and clinical outcomes in the diabetes control and complications trial. Diabetes. 2014;63(2):739–48.
84. Alanazi YA, et al. Role of autophagy in type 2 diabetes mellitus: the metabolic clash. J Cell Mol Med. 2024;28(23):e70240.
85. Yang J-S, et al. Autophagy and its link to type II diabetes mellitus. Biomedicine. 2017;7(2):8.
86. Park J-M, Kim D-H. A paradigm shift: AMPK negatively regulates ULK1 activity. Autophagy. 2024;20(4):960–2.
87. Liu W-J, et al. The activity and role of autophagy in the pathogenesis of diabetic nephropathy. Eur Rev Med Pharmacol Sci. 2018. https://doi.org/10.26355/eurrev.
88. Watada H, Fujitani Y. Minireview: autophagy in pancreatic β-cells and its implication in diabetes. Mol Endocrinol. 2015;29(3):338–48.
89. Zhang Z, et al. Exosomes derived from human umbilical cord mesenchymal stem cells (HUCMSC-EXO) regulate autophagy through AMPK-ULK1 signaling pathway to ameliorate diabetic cardiomyopathy. Biochem Biophys Res Commun. 2022;632:195–203.

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