ISSN 2524 – 0684 **e-ISSN 2524 – 0692**

UDC 616.379-008.64-085.361.4
IRSTI 76.03.55
DOI: 10.53065/kaznmu.2025.75.4.102

Received: 08.09.2025
Accepted for publication: 28.10.2025

PERINATAL MESENCHYMAL STEM CELLS AND THEIR CELL-FREE DERIVATIVES IN TYPE 1 AND TYPE 2 DIABETES: A SYSTEMATIC REVIEW

A.M. GANINA [1], A.A. AKHAEVA [1], A.ZH. ZHUNUSOV [1], A.KH. ZHAKUPOVA [1], O.V. ULYANOVA [1], L.V. KOZINA [1], I.R. FAKHRADIYEV [2]

[1] JSC «National Scientific Medical Center», Astana, Kazakhstan
[2] NPJSC «S.D. Asfendiyarov Kazakh National Medical University», Almaty, Kazakhstan

Abstract

Introduction. Type 1 and type 2 diabetes mellitus remain among the leading causes of morbidity and mortality, and a substantial proportion of patients do not achieve target HbA1c levels even with modern pharmacotherapy. Perinatal mesenchymal stromal cells (MSCs) and their cell-free derivatives have pronounced immunomodulatory and trophic effects and are considered a promising approach to modifying the course of diabetes.

Aim. To systematize clinical data on the use of perinatal MSCs in T1DM and T2DM and to summarize preclinical results on perinatal cell-free MSC products (exosomes, small extracellular vesicles, secretome, conditioned medium) in diabetes and its complications.

Materials and Methods. This systematic review was conducted in accordance with PRISMA 2020 recommendations. A search was performed in major international biomedical databases for the period from January 2000 to 3 October 2025 without language restrictions. We included clinical studies of T1DM/T2DM using perinatal MSCs or their cell-free derivatives with diabetes-oriented outcomes, as well as preclinical studies in diabetes models using perinatal exosomes, extracellular vesicles, secretome, or conditioned medium.

Results. Fourteen studies (6 clinical, 8 preclinical) were included in the review. Meta-analyses of randomized trials showed that MSC therapy, including perinatal sources, reduces HbA1c by ~1 percentage point, decreases insulin dose, and increases C-peptide without increasing the incidence of serious adverse events. Clinical studies of perinatal MSCs in T2DM demonstrate a 1–3% reduction in HbA1c and a 30–50% decrease in insulin requirements, along with improvement in insulin resistance parameters. Preclinical studies have shown that perinatal exosomes, small extracellular vesicles, and secretome improve insulin resistance, protect β-cells, accelerate healing of diabetic wounds, and provide nephro- and retinoprotective effects. No clinical studies of perinatal cell-free products in diabetes were identified at the time of the search.

Conclusion. Perinatal MSCs, primarily UC-MSCs, in clinical studies provide a moderate but clinically meaningful improvement in glycemic control in T1DM and T2DM with favorable short-term safety. Preclinical data on perinatal cell-free derivatives confirm the key role of paracrine mechanisms and the promise of standardized cell-free preparations, which requires confirmation in randomized clinical trials.

Key words: type 1 diabetes mellitus, type 2 diabetes mellitus, mesenchymal stem/stromal cells, umbilical cord mesenchymal stem cells, extracellular vesicles, cell- and tissue-based therapy.

ISSN 2524 – 0684 e-ISSN 2524 – 0692

Introduction. Type 1 and type 2 diabetes mellitus remain among the leading causes of morbidity and mortality worldwide [1, 2]. Despite advances in insulin therapy and the introduction of GLP-1 receptor agonists, SGLT2 inhibitors, and other modern agents, a substantial proportion of patients do not achieve target HbA1c levels and continue to accumulate microvascular and macrovascular complications [3, 4].

Mesenchymal stem/stromal cells possess immunosuppressive, anti-inflammatory, proangiogenic and trophic properties, which makes them attractive candidates for modifying the course of diabetes [4, 5]. Perinatal tissues (umbilical cord, Wharton's jelly, placenta, amniotic membrane) are ethically accessible sources of MSCs with high proliferative activity and a potent secretory profile [6-8].

A number of studies suggest that a significant part of the therapeutic effect of MSCs is mediated through paracrine factors and extracellular vesicles, rather than through long-term engraftment of the cells [9-11]. This served as an impetus for the development of cell-free approaches – exosomes, small extracellular vesicles (sEVs), secretome and conditioned medium [12].

Recent meta-analyses have demonstrated that the administration of MSCs in T1D and T2D leads to a decrease in HbA1c and insulin requirement, as well as an improvement in C-peptide levels [13, 14], however, the data aggregate various sources of MSCs (bone marrow, adipose tissue, umbilical cord, etc.) and do not focus on perinatal tissues and their cell-free derivatives.

In this regard, the aim of the present systematic review is to synthesize data from clinical studies of perinatal MSCs in T1D and T2D and to summarize preclinical information on perinatal cell-free MSC products (exosomes, secretome, conditioned medium) in diabetes and its complications.

Materials and methods. The review was conducted in accordance with the PRISMA 2020 recommendations for systematic reviews and meta-analyses [15]. Formal registration of the protocol in PROSPERO was not performed; however, prior to the start of the search, the inclusion and exclusion criteria, the list of databases, and the overall analysis strategy were predefined.

Information sources and search strategy

A systematic literature search was conducted in PubMed/MEDLINE, Web of Science Core Collection, Scopus, and the Cochrane Library (CENTRAL) for the period from January 2000 to 3 October 2025. The choice of the lower time limit (2000) was driven by the emergence in the early 2000s of key publications that for the first time systematically characterized perinatal MSCs, including placental and umbilical cord MSCs [16, 17].

Combinations of controlled MeSH terms [18] and free-text terms were used. Examples of search strategies were adapted for each database:

– for clinical studies:

("mesenchymal stem cell*" OR "MSC*" OR "mesenchymal stromal cell*")

AND ("umbilical cord" OR "Wharton's jelly" OR "placent*" OR "amniotic" OR "perinatal")

AND ("diabetes mellitus" OR "type 1 diabetes" OR "type 2 diabetes")

AND ("randomized" OR "clinical trial" OR "cohort" OR "case series");

- for cell-free approaches:

("exosome*" OR "extracellular vesicle*" OR "small extracellular vesicle*" OR "secretome" OR "conditioned medium")

AND ("umbilical cord mesenchymal stem cell*" OR "perinatal mesenchymal stem cell*")

ISSN 2524 – 0684 e-ISSN 2524 – 0692

AND (“diabetes” OR “diabetic rat*” OR “type 2 diabetes model”).

No language restrictions were applied; articles in other languages with an English abstract were included if sufficient information was available for data extraction.

Additionally, a manual search was performed through the reference lists of relevant clinical studies and meta-analyses on MSCs in diabetes and of key reviews on MSC-derived exosomes and secretome in diabetes and its complications.

When relevant records were identified, clinical trial registries (e.g., ClinicalTrials.gov) were also screened; however, only studies with published results were included in the analysis. No language restrictions were applied, and articles in other languages were included if an English abstract or sufficient data for extraction were available. In addition to the formal database search, the reference lists of relevant clinical studies and meta-analyses on MSC therapy in diabetes, as well as key reviews devoted to MSC-derived exosomes and secretome, were manually analyzed. When relevant entries were identified, clinical trial registries were reviewed; however, only studies with published results were included in the review.

Inclusion and exclusion criteria

The inclusion criteria for clinical studies were: a confirmed diagnosis of type 1 or type 2 diabetes mellitus, the use of perinatal MSCs (umbilical cord, placental, amniotic, or fetal) or perinatal cell-free MSC derivatives as an intervention, the presence of diabetes-related outcomes (such as HbA1c, fasting and postprandial blood glucose, C-peptide level, insulin and oral hypoglycemic drug requirements, parameters of β-cell function, or indicators of diabetic complications), and a study design in the form of RCTs, controlled non-randomized studies, cohort observations, or case series including at least five patients. The preclinical part of the review included studies on animal models of type 1 or type 2 diabetes and their complications, in which perinatal exosomes, extracellular vesicles, secretome, or conditioned medium from MSCs were used as the intervention.

Studies were excluded if they investigated only bone marrow–derived or adipose tissue–derived MSCs without a perinatal component, purely in vitro experiments without diabetic models, single clinical case reports (fewer than five patients), review articles without original data, and conference abstracts in the absence of a full-text publication.

Study selection and data extraction

Study selection was performed by two independent reviewers. At the first stage, they screened the titles and abstracts of all records for relevance to the review topic and to the predefined inclusion and exclusion criteria. At the second stage, the same reviewers assessed the full texts of potentially relevant articles. Disagreements in study selection were resolved through discussion until consensus was reached; if necessary, a third expert was consulted.

For all included clinical studies, data were extracted into a standardized form, capturing the following variables: type of diabetes (T1DM/T2DM), age and key demographic characteristics, disease duration, baseline and follow-up HbA1c values, glycemic control parameters (fasting and postprandial blood glucose, C-peptide level), daily insulin dose and/or oral hypoglycemic drug use, characteristics of the intervention (perinatal MSC source, total dose and dose per infusion, number of infusions, regimen and route of administration), follow-up duration, and the frequency and nature of adverse events and serious adverse events.

For non-randomized clinical studies, additional information was recorded on inclusion and exclusion criteria, sampling methods, and the presence or absence of a comparable control group.

ISSN 2524 – 0684 e-ISSN 2524 – 0692

In preclinical studies, the following were recorded: animal species and model, type and perinatal source of the cell-free product (exosomes, small extracellular vesicles, secretome, conditioned medium), dose and administration regimen, key metabolic outcomes (glycemia, HbA1c, markers of insulin resistance) and organ-specific outcomes (wound healing rate, nephro- and retinoprotective effects, etc.), as well as the proposed mechanisms of action.

At the identification stage, a total of 1,400 records were obtained through systematic searching: from PubMed/MEDLINE (n = 520), Web of Science Core Collection (n = 380), Scopus (n = 410) and Cochrane CENTRAL (n = 60), as well as from clinical trial registries (ClinicalTrials.gov and others) (n = 30). Before screening, 420 duplicates and 20 records were removed for technical reasons (incomplete bibliographic data, non-original materials, etc.), leaving 960 records for title and abstract screening.

At the title and abstract screening stage, 960 records were assessed for relevance to the review topic; 870 publications were excluded as non-relevant (absence of diabetes or a diabetic model, absence of MSCs or a perinatal source, review articles without original data). Ninety articles were selected for full-text assessment, of which 4 full texts could not be retrieved (e.g., due to journal inaccessibility or lack of response from authors). Thus, 86 studies were subjected to full-text evaluation. After detailed analysis, 72 articles were excluded for the following reasons:

– use of only bone marrow–derived or adipose tissue–derived MSCs without a perinatal component (n = 25);

– exclusively in vitro experiments without a diabetic animal model (n = 20);

– absence of diabetes-related outcomes (HbA1c, blood glucose, C-peptide, indicators of diabetic complications, etc.) (n = 15);

– reviews, commentaries, conference abstracts without full-text publication, or duplicate data from previously included studies (n = 12).

The final qualitative analysis included 14 studies, of which 6 were clinical (2 meta-analyses of RCTs and 4 primary clinical studies of perinatal MSCs in T2DM) and 8 were preclinical studies focusing on perinatal cell-free MSC derivatives (exosomes, small extracellular vesicles, secretome, conditioned medium) in models of T2DM and its complications. For the meta-analyses, data were extracted on the number of included RCTs, total sample size, MSC sources and key pooled effects on HbA1c, C-peptide, insulin dose, fasting blood glucose, and safety profile, as well as heterogeneity indices and subgroup analysis results by type of diabetes and MSC source. For primary clinical studies of perinatal MSCs, the following were recorded separately: design, country, inclusion criteria, type of diabetes, age and disease duration, characteristics of the perinatal cell source, doses and number of administrations, route of administration, follow-up duration, changes in glycemic control and β-cell function parameters, and the frequency and nature of adverse events. Preclinical studies were analyzed according to model type, source and type of the cell-free product, dosing, routes of administration, key metabolic and tissue outcomes, and proposed mechanisms of action (Figure 1).

ISSN 2524 – 0684 e-ISSN 2524 – 0692

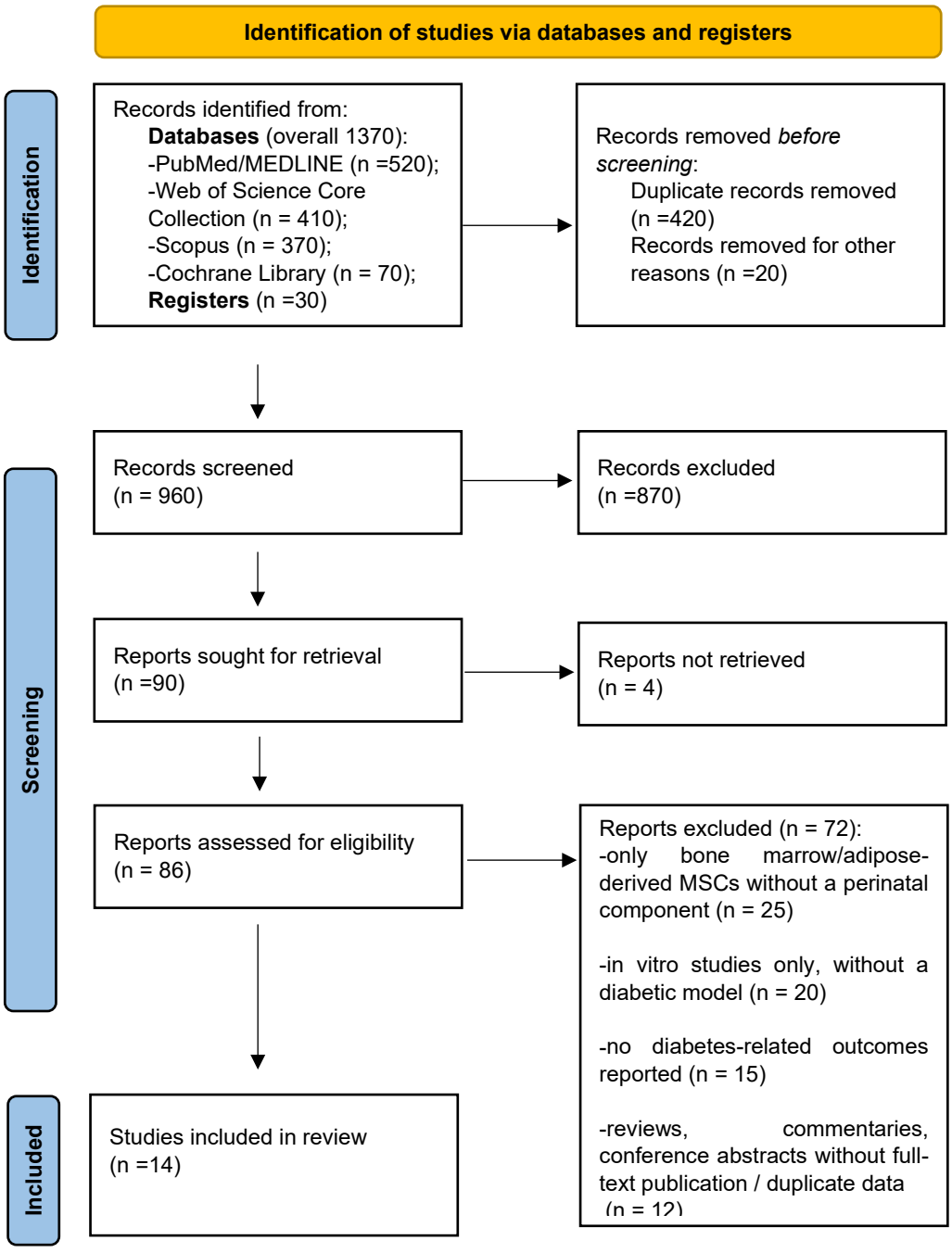

Figure 1. Flow diagram of study selection according to PRISMA 2020

Risk of bias assessment

Risk of bias assessment for randomized controlled trials (RCTs) was based on the results presented in meta-analyses performed using the Cochrane RoB 2 tool [19]. For randomized studies not included in these meta-analyses, a qualitative assessment was conducted of the adequacy of

ISSN 2524 – 0684 e-ISSN 2524 – 0692

randomization and allocation concealment, blinding, completeness of follow-up, and risk of selective reporting.

For non-randomized clinical studies, the risk of bias was assessed using the ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) tool [20]. The analysis was performed for the following domains: bias due to confounding; bias in selection of participants; bias in classification of interventions; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of outcomes; bias in selection of the reported result. For each domain, the risk of bias was classified as low, moderate, serious, or critical. The overall risk of bias for an individual study was determined by the worst judgement in any of the domains, provided that the majority of the remaining domains did not have a lower level of risk.

Results

General characteristics of the included studies

As a result of the systematic search and two-stage selection process, 14 studies meeting the review criteria were included. Of these, 6 were clinical studies of perinatal MSCs in type 1 and type 2 diabetes mellitus (T1DM and T2DM), including two meta-analyses of randomized clinical trials [21, 22] and four primary clinical studies of perinatal MSCs in patients with T2DM [23-26]. The remaining 8 studies were preclinical and focused on perinatal cell-free MSC derivatives (exosomes, small extracellular vesicles, secretome and conditioned medium) in models of T2DM and its complications - diabetic wounds, diabetic nephropathy and retinopathy [27-34].

Clinical studies geographically covered China, Indonesia, Malaysia and other Asian countries [23-26]. The included patients were predominantly middle-aged adults with T2DM duration ranging from several to more than 10 years; a separate pilot study evaluated placental MSCs in patients with severe insulin-dependent T2DM [26]. The meta-analyses included both T1DM and T2DM patients, which made it possible to partially assess potential differences in effects by diabetes type [21, 22]. In all clinical studies, perinatal MSCs were administered intravenously, as a single or repeated infusion, followed by 3 to 12 months of follow-up (Table 1).

Table 1. Clinical studies of perinatal MSCs in type 1 and type 2 diabetes mellitus (n = 6)

№	Authors, year	Study type	Population	Perinatal source	Main outcomes	Brief result / conclusion
1	Kashbour M. et al., 2025 [21]	Systematic review and meta-analysis of RCTs of MSCs in T1DM/T2DM	Patients with T1DM and T2DM (13 RCTs, n = 507; 199 T1DM, 308 T2DM)	MSCs from various sources, including umbilical cord	HbA1c, C-peptide, daily insulin dose, fasting glycemia, AEs	MSC therapy reduces HbA1c by about 0,72 percentage points, decreases insulin dose by ≈14,5 units/day and increases C-peptide without an increase in the rate of serious AEs

ISSN 2524 – 0684 **e-ISSN 2524 – 0692**

2	Nada A.H. et al., 2025 [22]	Systematic review and meta-analysis of RCTs of UC-MSCs	Patients with T1DM and T2DM (8 RCTs, n = 334; 172/162)	Umbilical cord MSCs (UC-MSCs)	HbA1c, C-peptide, daily insulin dose, AEs	UC-MSCs reduce HbA1c by about 1,06 percentage points, decrease insulin requirements (especially in T1DM); no serious AEs were reported
3	Zang L. et al., 2022 [23]	RCT, double-blind, placebo-controlled	Adults with insulin-dependent T2DM (n = 91: 61 UC-MSC, 30 placebo)	UC-MSCs (3 i.v. infusions of 1×10^6 cells/kg at 4-week intervals)	HbA1c, daily insulin dose, insulin resistance (euglycemic clamp)	In the UC-MSC group, HbA1c <7% and ≥50% reduction in insulin dose were more often achieved (20% vs 4,6%); HbA1c decreased by ~−1,3% vs −0,6% in the placebo group; improvement in insulin resistance; no serious AEs
4	Lian X.F. et al., 2022 [24]	Open-label prospective study	Patients with T2DM (n = 16)	hUC-MSCs (3 weekly i.v. infusions of 1×10^6 cells/kg)	Glycemia, HbA1c, HOMA-β, doses of glucose-lowering drugs	After three infusions of hUC-MSCs, a decrease in glycemia and HbA1c, improvement of HOMA-β and reduction of doses of glucose-lowering drugs were observed in some patients; no serious adverse

ISSN 2524 – 0684 e-ISSN 2524 – 0692

						events were recorded
5	Chin S.P. et al., 2025 [25]	Retrospective registry-based observational study	Patients with T2DM (n = 218; subgroup n = 83 with 12-month follow-up)	Allogeneic UC-MSCs (single i.v. infusion of 50–100×10⁶ cells)	HbA1c, insulin resistance indices (insulin, HOMA-IR), lipid profile, liver and kidney function, inflammatory markers	At 6 and 12 months, a decrease in HbA1c, improvement in insulin resistance and lipid profile, reduction in inflammatory markers, and improvement in liver and kidney tests were observed; no serious adverse events related to UC-MSC infusion were identified
6	Jiang X.X. et al., 2011 [26]	Open-label pilot study	Patients with severe insulin-dependent T2DM (n = 10)	Placental MSCs (3 i.v. infusions ~1–1,5×10⁶ cells/kg at 1-month intervals)	HbA1c, C-peptide, daily insulin dose	Daily insulin dose decreased from 63,7 ± 18,7 to 34,7 ± 13,4 units/day ($p<0,01$), in 4/10 patients by more than 50%; HbA1c decreased from ~9,8 to ~6,7%, C-peptide increased; no serious AEs or organ toxicity were detected

Preclinical studies included T2DM models in rats and mice (diet-induced or streptozotocin-induced diabetes), as well as models of diabetic complications: chronic skin wounds, diabetic nephropathy, and retinopathy [27-34]. Perinatal MSC sources included umbilical cord (hUC-MSC), Wharton's jelly, placenta, and amniotic membrane; both purified exosomes/small extracellular vesicles and secretome/conditioned medium were evaluated (Table 2).

ISSN 2524 – 0684 e-ISSN 2524 – 0692

Table 2. Preclinical studies of perinatal cell-free MSC derivatives in diabetes mellitus and its complications (n = 8)

№	Authors, year	Study type	Population	Perinatal source	Main outcomes	Brief result / conclusion
1	Sun Y. et al., 2018 [27]	Preclinical in vivo study	Rats with induced type 2 diabetes	Exosomes derived from human UC-MSC	Glycemia, glucose tolerance test, IRS-1/PI3K/Akt signaling, GLUT4 expression/translocation, β-cell apoptosis	UC-MSC exosomes reduce glycemia, improve glucose tolerance and insulin sensitivity, restore IRS-1/Akt signaling, enhance GLUT4 translocation, and protect β-cells from apoptosis
2	Yap S.K. et al., 2022 [28]	Preclinical in vivo study	Rats with a type 2 diabetes model	Small extracellular vesicles (sEV) from UC-MSC	HbA1c, glycemia, insulin resistance, morphology of the pancreas, liver, and kidneys	UC-MSC sEV improve insulin resistance, decrease HbA1c and glycemia, and normalize the histological structure of the pancreas and target organs without signs of hepato- or nephrotoxicity
3	Widyaningsih / Wulandari et al. [29]	Preclinical in vivo study	Rats with a type 2 diabetes model	Secretome of hypoxia-preconditioned MSCs	Glycemia, markers of oxidative stress and inflammation, histology of the pancreas and liver	MSC secretome reduces hyperglycemia, decreases oxidative stress and inflammation (reduced IL-6 and shift of macrophages toward the M2 phenotype (CD163)), and improves the histological picture of the

ISSN 2524 – 0684 e-ISSN 2524 – 0692

						pancreas and liver
4	Hendrawan S. et al., 2021 [30]	Preclinical in vitro + in vivo study	Cell models and animals with diabetic wounds	Conditioned medium (CM) from hUC-MSC	Wound healing rate, epithelialization, collagen formation	hUC-MSC conditioned medium accelerates healing of diabetic wounds, improves epithelialization and collagen formation, confirming the therapeutic potential of the secretome
5	Ormazabal V. et al., 2022 [31]	Preclinical in vivo study	Mice with type 2 diabetes and diabetic wounds	Secretome of endothelial cells differentiated from MSCs (perinatal source)	Wound healing rate, vascular density, tissue perfusion	Secretome of endothelial MSC derivatives accelerates wound closure, enhances angiogenesis, and improves microvascular perfusion under diabetic conditions
6	Yang J. et al., 2020 [32]	Preclinical in vivo study	Rats with chronic diabetic wounds	hUC-MSC exosomes incorporated into a PF-127 gel	Wound closure rate, structure of granulation tissue, inflammatory markers	Combination of hUC-MSC exos + PF-127 gel significantly accelerates healing of diabetic wounds, improves the quality of granulation tissue, and reduces the level of inflammation
7	Wang Y. et al., 2023 [33]	Preclinical in vivo and in	Mouse models of diabetic kidney	Exosomes derived from human UC-	Proteinuria, renal function parameters, inflammatory and	hUC-MSC-Exo attenuate manifestations of DKD, reduce

ISSN 2524 – 0684 e-ISSN 2524 – 0692

		vitro study	disease (DKD) and cell models	MSC (hUC-MSC-Exo)	fibrotic markers, NLRP3 inflammasome	inflammation and activation of the NLRP3 inflammasome, protect renal tissue, and reduce fibrosis
8	Kim H. et al., 2023 [34]	Preclinical in vivo study	Rats with diabetic retinopathy (preventive model)	Exosome-enriched conditioned medium (ERCM) from amniotic membrane stem cells	Vascular permeability, inflammatory markers, retinal morphology	ERCM from amniotic stem cells prevents or alleviates the development of signs of diabetic retinopathy, reduces inflammation and vascular permeability in the retina

Clinical studies of perinatal MSCs in T1DM and T2DM

Meta-analyses of randomized clinical trials

The meta-analysis by Kashbour et al. included 13 randomized controlled trials with a total of 507 patients (199 with T1DM and 308 with T2DM), in which MSCs from various sources were used, including perinatal MSCs [21]. Compared with standard therapy, MSC therapy was associated with a reduction in HbA1c by 0.72 percentage points, a decrease in the daily insulin dose by approximately 14.6 IU/day, and an increase in C-peptide levels. At the same time, no significant changes in fasting glycemia were noted, which indicates a predominant effect on long-term glycemic control and β-cell function. The frequency of serious adverse events did not differ from the control group, and the reported adverse effects were mild or moderate and self-limiting (hypoglycemic episodes in the context of insulin dose reduction, transient local reactions) [21].

The meta-analysis by Nada et al. focused exclusively on umbilical cord MSCs (UC-MSCs) and included 8 randomized clinical trials involving 334 patients (172 in the UC-MSC groups and 162 in the control groups) [22]. In this analysis, the reduction in HbA1c was more pronounced and amounted to 1.06 percentage points, which may reflect a more homogeneous population and a single perinatal cell source. UC-MSCs also significantly reduced insulin requirements, especially in patients with T1DM, and increased C-peptide levels, which is consistent with the assumption of partial preservation or restoration of β-cell function. The safety profile was assessed as favorable: no serious adverse events related to the intervention were identified, and the overall incidence of adverse events did not differ from the control [22]. Both meta-analyses noted substantial methodological heterogeneity of the primary studies (differences in MSC sources, doses, administration regimens, and concomitant therapy protocols), which limits the possibility of formulating standardized recommendations for clinical use.

Primary clinical studies in T2DM

Randomized double-blind placebo-controlled trial by Zang et al. evaluated the efficacy of three intravenous infusions of UC-MSCs (1×10^6 cells/kg at 4-week intervals) in 91 adult patients

ISSN 2524 – 0684 e-ISSN 2524 – 0692

with insulin-dependent T2DM [23]. At 12 months of follow-up, the UC-MSC group more frequently achieved the combined goals of HbA1c <7% and ≥50% reduction in daily insulin dose compared with placebo (20% vs. 4.6%). The mean reduction in HbA1c was about 1.3% in the UC-MSC group and 0.6% in the placebo group, with improvement in insulin resistance indices (according to euglycemic clamp data) [23]. No serious adverse events were recorded; most side effects were mild and transient.

In an open prospective study by Lian et al., 16 patients with T2DM received three weekly intravenous infusions of hUC-MSCs at a dose of 1×10^6 cells/kg [24]. Over 12 months of follow-up, some patients showed reductions in glycemia and HbA1c, improvement in the HOMA-β index, and decreases in doses of glucose-lowering medications. Although the lack of a control group and the small sample size do not allow definitive conclusions about the magnitude of the effect, the results support the potential ability of UC-MSCs to improve β-cell function and glycemic control in patients with T2DM [24].

A retrospective registry study by Chin et al. included 218 patients with T2DM who received a single infusion of allogeneic UC-MSCs ($50–100\times10^6$ cells), with outcomes assessed at 6 and 12 months [25]. Patients showed reductions in HbA1c, improvement in insulin resistance parameters (insulin, HOMA-IR), favorable changes in lipid profile, as well as improved liver and kidney function and reduced inflammatory markers. No serious adverse events that could be attributed to the UC-MSC infusion were recorded [25]. Despite the observational nature of the study and the possible influence of concomitant therapy, these real-world data complement the results of RCTs, indicating the potential efficacy and safety of UC-MSCs in T2DM.

A special place is occupied by a pilot open study by Jiang et al., in which 10 patients with severe insulin-dependent T2DM received three intravenous infusions of placental MSCs at 1-month intervals [26]. By 6 months of follow-up, the daily insulin dose decreased on average from 63.7 ± 18.7 to 34.7 ± 13.4 IU/day ($p<0.01$), with four patients experiencing a reduction in dose of more than 50%. HbA1c decreased from approximately 9.8 to 6.7%, and C-peptide levels increased [26]. At the same time, there were no signs of hepato- or nephrotoxicity, severe infusion reactions, or other serious complications, which underscores the potential safety of placental MSCs even in severely ill patients.

In all clinical studies, common limitations included small sample sizes, variability in doses and administration regimens, lack of standardized long-term safety monitoring, and, in some cases, absence of control groups. Clinical studies in which patients with T1DM or T2DM would receive perinatal cell-free MSC-derived products (exosomes, secretome, conditioned medium) were not identified at the time of the search.

Preclinical studies of perinatal cell-free MSC derivatives

Exosomes and small extracellular vesicles in T2DM

In the study by Sun et al., exosomes isolated from hUC-MSCs were administered to rats with a model of T2DM [27]. The treatment was accompanied by a reduction in glycemia and improvement in glucose tolerance test results, restoration of IRS-1/PI3K/Akt signaling pathways, enhanced GLUT4 translocation, and decreased β-cell apoptosis. These data support the concept that perinatal MSC-derived exosomes are capable of simultaneously improving insulin sensitivity of peripheral tissues and protecting β-cells.

The preclinical study by Yap et al. showed that small extracellular vesicles (small EVs) obtained from hUC-MSCs in a rat model of T2DM reduce HbA1c and glycemia, improve insulin resistance, and normalize the morphology of the pancreas, liver, and kidneys without signs of

ISSN 2524 – 0684 e-ISSN 2524 – 0692

hepato- or nephrotoxicity [28]. Thus, the effects of small EVs are generally consistent with the results for exosomes, indicating a key role of perinatal extracellular vesicles in the modulation of metabolism and organ protection in T2DM.

The secretome of hypoxically preconditioned MSCs in the study by Widyaningsih et al. also demonstrated a pronounced antihyperglycemic and anti-inflammatory effect in rats with a T2DM model: blood glucose levels decreased, markers of oxidative stress and inflammation (including IL-6) were reduced, a shift of macrophages toward the anti-inflammatory M2 phenotype (CD163) was observed, and the histological picture of the pancreas and liver improved [29]. hese results underscore the importance of optimizing MSC preconditioning conditions to enhance their secretory potential.

Perinatal cell-free products in diabetic wounds

A number of studies have evaluated the effects of perinatal MSC-derived cell-free products on the healing of diabetic wounds. Hendrawan et al. showed that hUC-MSC-conditioned medium accelerates the healing of skin wounds in rats with induced diabetes by increasing the rate of wound area contraction, improving re-epithelialization and collagen formation according to histological analysis [30]. These effects were accompanied by improved quality of granulation tissue without signs of local or systemic toxicity.

Ormazábal et al. used the secretome of endothelial cells differentiated from perinatal MSCs in a model of diabetic wounds in mice with type 2 diabetes [31]. The secretome accelerated wound closure, improved the structure of the newly formed skin and was enriched with angiogenic factors (VEGF-C, Ang-1/Ang-2, FGF-7, MMP-9), indicating an indirect enhancement of angiogenesis and microvascular perfusion under diabetic conditions.

Yang et al. demonstrated that hUC-MSC-derived exosomes incorporated into the thermosensitive hydrogel Pluronic F127 significantly accelerate the healing of chronic diabetic wounds in rats, promote the formation of higher-quality granulation tissue, increase vascular density and reduce the severity of inflammation; in a number of cases, the regenerated skin was structurally close to normal [32]. The combined use of the hydrogel and exosomes provided more prolonged local release of biologically active factors compared with administration of exosomes alone.

Exosomes of perinatal MSCs in diabetic nephropathy

In the study by Wang et al., exosomes from hUC-MSCs were investigated in in vivo and in vitro models of diabetic nephropathy (DKD) [33]. Administration of HUC-MSC-Exo to mice with DKD led to a reduction in proteinuria, improvement of renal function parameters, decreased inflammation and fibrosis, as well as suppression of NLRP3 inflammasome activation in kidney tissue. In cell models, a decrease in apoptosis and inflammatory signaling was observed. These data indicate that perinatal MSC-derived exosomes may represent a promising cell-free approach to the prevention and treatment of diabetic nephropathy.

Exosome-enriched conditioned medium in diabetic retinopathy

The study by Kim et al. focused on the preventive effects of exosome-enriched conditioned medium (ERCM) from the amniotic membrane in a rat model of diabetic retinopathy [34]. Subconjunctival administration of ERCM reduced vascular permeability and inflammation in the retina, slowed the development of typical morphological features of diabetic retinopathy, and partially preserved functional parameters according to electroretinography. These results demonstrate the potential of perinatal cell-free products for protecting target organs in diabetes - in this case, the neural retina and microvessels of the eye.

ISSN 2524 – 0684 e-ISSN 2524 – 0692

Risk of bias assessment using ROBINS-I

Risk of bias assessment using ROBINS-I showed that all three non-randomized studies had at least a serious risk of bias due to confounding and selection of participants. In the studies by Lian et al. [24] and Jiang et al. [26] this was due to the absence of a control group, open-label design and small sample size, while in the registry study by Chin et al. [25] it was related to the retrospective nature of the study and incomplete 12-month follow-up data. At the same time, the interventions were clearly classified, and the outcomes were measured using objective laboratory methods, which reduced the risk of bias in the corresponding domains. Overall, all three studies were classified as having a serious overall risk of bias, which should be taken into account when interpreting their results (Table 3).

Table 3. Assessment of risk of bias in non-randomized clinical studies using the ROBINS-I tool

ROBINS-I domain	Lian et al., 2022 [24] (n=16)	Chin et al., 2025 [25] (n=218)	Jiang Jiang et al., 2011 [26] (n=10)
Bias due to confounding	Serious – no control, possible changes in standard therapy	Serious – no control, possible physician-driven patient selection	Serious – severely ill patients, no comparable group
Bias in selection of participants	Serious – convenience sample, small n	Serious – retrospective inclusion, incomplete registry cohort	Serious – pilot study, inclusion based on clinical appropriateness
Classification of interventions	Low – administration regimen standardized	Low – single infusion of 50–100×10⁶ UC-MSC	Low – homogeneous regimen of three infusions
Deviations from intended interventions	Moderate – open-label design, possible changes in patient behavior	Moderate – concomitant therapy varies	Moderate – open-label design, possible adaptations of therapy
Missing data	Moderate – limited sample size, potential losses	Serious – not all patients had 12-month data	Moderate – short follow-up, possible missing data
Measurement of outcomes	Low – objective laboratory parameters	Low – routine standardized measurements	Low – HbA1c, C-peptide, insulin doses are objective
Selection of reported results	Moderate – open-label design, risk of selective reporting	Moderate/serious – retrospective analysis, partial reporting	Moderate – pilot without prespecified protocol
Overall risk of bias	Serious	Serious	Serious

Discussion. The present systematic review has shown that perinatal mesenchymal stem/stromal cells, predominantly umbilical cord–derived (UC-MSCs), provide a moderate but clinically meaningful improvement in glycemic control and β-cell function parameters in patients

ISSN 2524 – 0684 e-ISSN 2524 – 0692

with T1DM and T2DM, with a favorable short-term safety profile. At the same time, the evidence base for perinatal cell-free MSC derivatives (exosomes, small extracellular vesicles, secretome and conditioned medium) is limited to preclinical models and lacks clinical confirmation.

The pooled results of meta-analyses [21, 22] confirm that MSC therapy as a whole leads to a decrease in HbA1c, a reduction in insulin requirements, and an increase in C-peptide levels in patients with T1DM/T2DM. These data are generally consistent with earlier meta-analyses by He et al. [13] and Sun et al. [14], which also demonstrated improvement in glycemic control parameters with MSC use in patients with diabetes. However, those studies [13, 14] considered MSCs from various sources and did not perform a separate analysis of perinatal MSCs and their derivatives. In contrast, the present review focuses specifically on perinatal tissues and their cell-free products, which makes it possible to more clearly assess the contribution of this specific MSC population to the modification of T1DM/T2DM course and its complications. However, the meta-analysis by Kashbour et al. [21], which included MSCs from various sources (bone marrow, adipose tissue, umbilical cord, etc.), showed a more modest HbA1c reduction (~0.72 percentage points), whereas the meta-analysis by Nada et al., focused exclusively on UC-MSCs, demonstrated a more pronounced effect (~1.06 percentage points) [22]. This indirectly suggests that perinatal MSCs may have at least no lower, and possibly a more pronounced, efficacy on key diabetes-oriented outcomes compared with MSCs from other sources.

The first clinical studies of perinatal MSCs in T2DM [23-26] complement the meta-analytic data and allow the magnitude of the effect to be specified in real-world populations. In a randomized double-blind trial by Zang et al. [23] three intravenous infusions of UC-MSCs led to an HbA1c reduction of approximately 1.3% and a ≥50% decrease in daily insulin dose in a substantial proportion of patients compared with placebo. A pilot study of placental MSCs in patients with severe insulin-dependent T2DM [26] demonstrated comparable changes in magnitude: a decrease in HbA1c from ~9.8 to ~6.7% and more than a 50% reduction in insulin dose in a subset of patients. Observational registry data from Chin et al. [25] confirm that a single UC-MSC infusion is associated with sustained HbA1c reduction and improvement in insulin resistance over 6–12 months.

Taken together, these results are comparable in clinical relevance to the addition of another modern glucose-lowering agent, but MSC therapy acts simultaneously on several pathogenetic pathways–β-cell function, insulin resistance and chronic inflammation – whereas most pharmacological classes target a more limited spectrum of mechanisms. At the same time, it is important to emphasize that for T1DM the evidence base remains more fragmentary and is mainly based on meta-analytic pooling of heterogeneous studies [13, 14, 21, 22]. The more pronounced reduction in insulin requirements in the UC-MSC subgroups in the meta-analysis by Nada et al. [22] may indicate the potential for partial preservation of residual β-cell function with early intervention; however, the durability of this effect and its relationship to modification of the autoimmune process require long-term randomized studies. In contrast to T2DM, where perinatal MSCs mainly affect insulin resistance and residual β-cell secretory activity, in T1DM the key limitation remains the autoimmune component, which complicates data extrapolation.

Potential mechanisms and the role of perinatal origin

Perinatal tissues are characterized by high proliferative activity of MSCs, a more “young” phenotype, and a rich secretory profile compared with bone marrow– and adipose tissue–derived MSCs. This is reflected in preclinical studies of perinatal cell-free products. Exosomes and small extracellular vesicles derived from UC-MSCs in rat models of T2DM not only reduce glycemia

ISSN 2524 – 0684 e-ISSN 2524 – 0692

and HbA1c but also restore key elements of insulin signaling (IRS-1/PI3K/Akt, GLUT4 translocation) and protect β-cells from apoptosis [27, 28].

The secretome of hypoxia-preconditioned MSCs demonstrates a pronounced anti-inflammatory and antioxidant effect, accompanied by a shift of macrophages toward the M2 phenotype and improvement of pancreatic and hepatic morphology [29]. These data support the concept that a significant proportion of the therapeutic effects of perinatal MSCs is mediated through paracrine factors and extracellular vesicles rather than through long-term cell engraftment.

Preclinical studies on diabetic complications [30-34] also emphasize the pleiotropic effects of perinatal cell-free products: acceleration of diabetic wound healing with enhanced angiogenesis and remodeling of the extracellular matrix [30-32], a nephroprotective effect with suppression of inflammation and NLRP3 inflammasome activation in diabetic nephropathy [33], as well as reduced vascular permeability and inflammation in the retina in models of diabetic retinopathy [34]. The presence of effects on various target organs is consistent with the systemic nature of the paracrine action of perinatal MSCs and their derivatives.

Clinical significance and place in the therapy of T1D and T2D

From a practical standpoint, a reduction in HbA1c by 0.8–1.3% and a 30–50% decrease in insulin requirements over 6–12 months of follow-up with a favorable safety profile appear clinically meaningful, especially for patients with long-standing T2D and pronounced insulin resistance, in whom options for optimizing standard pharmacotherapy are limited. In T1D, the data are currently more fragmented and primarily based on meta-analytic pooling of different MSC sources [21, 22]. Nonetheless, the more pronounced reduction in insulin requirements in UC-MSC subgroups [22] may reflect the potential for partial preservation of residual β-cell function with early intervention.

At the same time, it is important to emphasize that most of the included clinical studies consider perinatal MSCs as an additional option to standard therapy rather than a replacement. At the current stage of evidence development, MSC therapy should be regarded as a potentially beneficial adjuvant approach in carefully selected high-risk patients, rather than as a universal solution for all individuals with T1D/T2D.

Prospects for cell-free perinatal products

Despite compelling preclinical data, no clinical studies were identified at the time of the search in which patients with T1D or T2D received perinatal exosomes, small extracellular vesicles, secretome, or conditioned medium. This reflects a substantial translational gap between the preclinical and clinical levels.

On the one hand, cell-free products offer potential advantages over whole-cell MSC preparations: simpler control over dose and composition, absence of the risk of uncontrolled cell proliferation and differentiation, and the possibility of industrial scale-up and standardization (for example, in the form of ready-to-use medicinal products for systemic or local administration). On the other hand, standardization of methods for isolation, purification, and quantitative assessment of exosomes and secretome remains an unresolved challenge. There are no generally accepted criteria of “potency” for such products, and the optimal doses, routes of administration, treatment frequency, and duration for different diabetes phenotypes and its complications have not been defined.

Furthermore, most preclinical studies use relatively short-term rodent models of diabetes with limited comparability to long-standing T2D and its complications in humans. This necessitates caution when extrapolating the obtained results to clinical practice.

ISSN 2524 – 0684 e-ISSN 2524 – 0692

Study limitations. Strengths and limitations. The present review is focused specifically on perinatal MSCs and their cell-free derivatives in T1D and T2D and integrates clinical data on whole-cell MSC therapy with preclinical results on exosomes and the secretome, which makes it possible to trace the potential transition from cell-based to cell-free approaches. At the same time, the available studies are limited by small sample sizes, heterogeneity of designs and dosages, short follow-up periods and incomplete assessment of long-term safety, whereas preclinical studies are characterized by variability of models, routes of administration, and insufficient standardization of exosome and secretome characteristics, without direct comparisons with MSCs from other sources.

Conclusion. The conducted systematic review showed that perinatal MSCs, primarily UC-MSCs, in clinical studies provide a moderate but clinically meaningful improvement in glycemic control and β-cell function in T1D and T2D against the background of a favorable short-term safety profile. Preclinical data on perinatal cell-free MSC derivatives (exosomes, small extracellular vesicles, secretome, conditioned medium) demonstrate pronounced metabolic and organ-protective effects and highlight the key role of paracrine mechanisms. Taken together, these findings indicate the promise of a transition from whole-cell perinatal MSC therapy to standardized cell-free products; however, the lack of clinical studies of cell-free derivatives and the methodological limitations of existing studies currently do not allow recommending them for routine practice. Large randomized trials with long-term follow-up and standardization of technologies for obtaining perinatal cellular and cell-free products are needed.

Conflict of interest. The authors declare no conflict of interest.

Authors' contribution. Concept, AG and AA; methodology, AZh; writing – preparation of the manuscript, AZh, AG, AA, AZh, OU, LK, IF; writing – review and editing, AZh, AG, AA, AZh, OU, LK, IF; project administration, AG; funding acquisition, AG. All authors have read and agreed to the published version of the manuscript. The authors declare that this material has not been previously published and is not under consideration by other publishers.

Funding. The study and manuscript were prepared within the framework of the grant-funded project BR28713159 «Innovative approaches to the development of a cell-based product for the therapy of chronic and socially significant diseases».

REFERENCES

1. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends. J Epidemiol Glob Health. 2020;10(1):107–111. https://doi.org/10.2991/jegh.k.191028.001
2. Ong KL, Stafford LK, McLaughlin SA, Boyko EJ, Vollset SE, Smith AE, et al. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2023;402(10397):203–234. https://doi.org/10.1016/S0140-6736(23)01301-6
3. Tegegne KD, Gebeyehu NA, Yirdaw LT, Yitayew YA, Kassaw MW. Determinants of poor glycemic control among type 2 diabetes in Ethiopia: a systematic review and meta-analysis. Front Public Health. 2024;12:1256024. https://doi.org/10.3389/fpubh.2024.1256024
4. Chan SP, Lim LL, Chan JCN, Matthews DR. Adjusting the Use of Glucose-Lowering Agents in the Real-World Clinical Management of People with Type 2 Diabetes: A Narrative Review. Diabetes Ther. 2023;14(5):823–838. https://doi.org/10.1007/s13300-023-01386-5
5. Miceli V, Bulati M, Iannolo G, Zito G, Gallo A, Conaldi PG. Therapeutic Properties of Mesenchymal Stromal/Stem Cells: The Need of Cell Priming for Cell-Free Therapies in Regenerative Medicine. Int J Mol Sci. 2021;22(2). https://doi.org/10.3390/ijms22020763
6. Alviano F, Fossati V, Marchionni C, Arpinati M, Bonsi L, Franchina M, et al. Term Amniotic membrane is a high throughput source for multipotent Mesenchymal Stem Cells with the

ISSN 2524 – 0684 e-ISSN 2524 – 0692

ability to differentiate into endothelial cells in vitro. BMC Dev Biol. 2007;7:11. https://doi.org/10.1186/1471-213X-7-11
7. Kim DW, Staples M, Shinozuka K, Pantcheva P, Kang SD, Borlongan CV. Wharton's jelly-derived mesenchymal stem cells: phenotypic characterization and optimizing their therapeutic potential for clinical applications. Int J Mol Sci. 2013;14(6):11692–11712. https://doi.org/10.3390/ijms140611692
8. Maraldi T, Russo V. Amniotic Fluid and Placental Membranes as Sources of Stem Cells: Progress and Challenges. Int J Mol Sci. 2022;23(10). https://doi.org/10.3390/ijms23105362
9. Kou M, Huang L, Yang J, Chiang Z, Chen S, Liu J, et al. Mesenchymal stem cell-derived extracellular vesicles for immunomodulation and regeneration: a next generation therapeutic tool? Cell Death Dis. 2022;13(7):580. https://doi.org/10.1038/s41419-022-05034-x
10. Vizoso FJ, Eiro N, Cid S, Schneider J, Perez-Fernandez R. Mesenchymal Stem Cell Secretome: Toward Cell-Free Therapeutic Strategies in Regenerative Medicine. Int J Mol Sci. 2017;18(9). https://doi.org/10.3390/ijms18091852
11. Bulut Ö, Gürsel İ. Mesenchymal stem cell derived extracellular vesicles: promising immunomodulators against autoimmune, autoinflammatory disorders and SARS-CoV-2 infection. Turk J Biol. 2020;44(3):273–282. https://doi.org/10.3906/biy-2002-79
12. Harrell CR, Fellabaum C, Jovicic N, Djonov V, Arsenijevic N, Volarevic V. Molecular Mechanisms Responsible for Therapeutic Potential of Mesenchymal Stem Cell-Derived Secretome. Cells. 2019;8(5). https://doi.org/10.3390/cells8050467
13. He J, Kong D, Yang Z, Guo R, Amponsah AE, Feng B, et al. Clinical efficacy on glycemic control and safety of mesenchymal stem cells in patients with diabetes mellitus: Systematic review and meta-analysis of RCT data. PLoS One. 2021;16(3):e0247662. https://doi.org/10.1371/journal.pone.0247662
14. Sun SY, Gao Y, Liu GJ, Li YK, Gao W, Ran XW. Efficacy and Safety of Stem Cell Therapy for T1DM: An Updated Systematic Review and Meta-Analysis. J Diabetes Res. 2020;2020:5740923. https://doi.org/10.1155/2020/5740923
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
16. Fukuchi Y, Nakajima H, Sugiyama D, Hirose I, Kitamura T, Tsuji K. Human placenta-derived cells have mesenchymal stem/progenitor cell potential. Stem Cells. 2004;22(5):649–658. https://doi.org/10.1634/stemcells.22-5-649
17. Wang HS, Hung SC, Peng ST, Huang CC, Wei HM, Guo YJ, et al. Mesenchymal stem cells in the Wharton's jelly of the human umbilical cord. Stem Cells. 2004;22(7):1330–1337. https://doi.org/10.1634/stemcells.2004-0013
18. Tugwell P, Knottnerus JA. Multimorbidity and Comorbidity are now separate MESH headings. J Clin Epidemiol. 2019;105:vi–viii. https://doi.org/10.1016/j.jclinepi.2018.11.019
19. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. https://doi.org/10.1136/bmj.l4898
20. Yuan M, Wu J, Lee J, Cao D, Huynh MN, Gallo L, et al. The risk of bias of non-randomized observational studies in deep inferior epigastric perforator flap breast reconstruction: A systematic review using ROBINS-I. J Plast Reconstr Aesthet Surg. 2022;75(11):4096–4105. https://doi.org/10.1016/j.bjps.2022.06.093

ISSN 2524 – 0684 **e-ISSN 2524 – 0692**

21. Kashbour M, Abdelmalik A, Yassin MNA, Abed M, Aldieb E, Abdullah DM, et al. Mesenchymal stem cell-based therapy for type 1 & 2 diabetes mellitus patients: a systematic review and meta-analysis of randomized controlled trials. Diabetol Metab Syndr. 2025;17:189. https://doi.org/10.1186/s13098-025-01619-6
22. Nada AH, Ibrahim IA, Oteri V, Shalabi L, Asar NK, Aqeilan SR, et al. Safety and efficacy of umbilical cord mesenchymal stem cells in the treatment of type 1 and type 2 diabetes mellitus: a systematic review and meta-analysis. Expert Rev Endocrinol Metab. 2025;20(2):107–117. https://doi.org/10.1080/17446651.2025.2457474
23. Zang L, Li Y, Hao H, Liu J, Cheng Y, Li B, et al. Efficacy and safety of umbilical cord-derived mesenchymal stem cells in Chinese adults with type 2 diabetes: a single-center, double-blinded, randomized, placebo-controlled phase II trial. Stem Cell Res Ther. 2022;13(1):180. https://doi.org/10.1186/s13287-022-02848-6
24. Lian XF, Lu DH, Liu HL, Liu YJ, Han XQ, Yang Y, et al. Effectiveness and safety of human umbilical cord-mesenchymal stem cells for treating type 2 diabetes mellitus. World J Diabetes. 2022;13(10):877–887. https://doi.org/10.4239/wjd.v13.i10.877
25. Chin SP, Kee LT, Mohd MA, Then KY. Umbilical Cord-Derived Mesenchymal Stem Cells Infusion in Type 2 Diabetes Mellitus Patients: A Retrospective Cytopeutics' Registry Study. Diabetes Metab Syndr Obes. 2025;18:1643–1659. https://doi.org/10.2147/dmso.S507801
26. Jiang R, Han Z, Zhuo G, Qu X, Li X, Wang X, et al. Transplantation of placenta-derived mesenchymal stem cells in type 2 diabetes: a pilot study. Front Med. 2011;5(1):94–100. https://doi.org/10.1007/s11684-011-0116-z
27. Sun Y, Shi H, Yin S, Ji C, Zhang X, Zhang B, 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):7613–7628. https://doi.org/10.1021/acsnano.7b07643
28. Yap SK, Tan KL, Abd Rahaman NY, Saulol Hamid NF, Ooi J, Tor YS, 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). https://doi.org/10.3390/pharmaceutics14030649
29. Widyaningsih W, Putra A, Priyantini S, Muhar AM, Sumarawati T, Trisnadi S, et al. Secretome of Hypoxia-Preconditioned Mesenchymal Stem Cells Ameliorates Hyperglycemia in Type 2 Diabetes Mellitus Rats. Trends Sci. 2024;21(5):7278. https://doi.org/10.48048/tis.2024.7278
30. Hendrawan S, Kusnadi Y, Lagonda CA, Fauza D, Lheman J, Budi E, et al. Wound healing potential of human umbilical cord mesenchymal stem cell conditioned medium: An in vitro and in vivo study in diabetes-induced rats. Vet World. 2021;14(8):2109–2117. https://doi.org/10.14202/vetworld.2021.2109-2117
31. Ormazabal V, Nova-Lampeti E, Rojas D, Zúñiga FA, Escudero C, Lagos P, et al. Secretome from Human Mesenchymal Stem Cells-Derived Endothelial Cells Promotes Wound Healing in a Type-2 Diabetes Mouse Model. Int J Mol Sci. 2022;23(2). https://doi.org/10.3390/ijms23020941
32. Yang J, Chen Z, Pan D, Li H, Shen J. Umbilical Cord-Derived Mesenchymal Stem Cell-Derived Exosomes Combined Pluronic F127 Hydrogel Promote Chronic Diabetic Wound Healing and Complete Skin Regeneration. Int J Nanomedicine. 2020;15:5911–5926. https://doi.org/10.2147/ijn.S249129

ISSN 2524 – 0684 **e-ISSN 2524 – 0692**

33. Wang Y, Liu J, Wang H, Lv S, Liu Q, Li S, et al. Mesenchymal Stem Cell-Derived Exosomes Ameliorate Diabetic Kidney Disease Through the NLRP3 Signaling Pathway. Stem Cells. 2023;41(4):368–383. https://doi.org/10.1093/stmcls/sxad010
34. Kim H, Goh YS, Park SE, Hwang J, Kang N, Jung JS, et al. Preventive Effects of Exosome-Rich Conditioned Medium From Amniotic Membrane-Derived Mesenchymal Stem Cells for Diabetic Retinopathy in Rats. Transl Vis Sci Technol. 2023;12(8):18. https://doi.org/10.1167/tvst.12.8.18

Information about authors

Anastasia Mikhailovna Ganina, Biotechnologist, Head of the Department of Cell Technologies and Transplantation, JSC National Scientific Medical Center, Astana, Kazakhstan, anastassiya_smelova@mail.ru, https://orcid.org/0000-0002-2047-1497.

Aizhan Abdisadikovna Akhaeva, Biotechnologist, PhD (Biology), Head of the Laboratory of Cellular Immunotherapy, JSC National Scientific Medical Center, Astana, Kazakhstan, akhaeva@mail.ru, https://orcid.org/0009-0007-4741-6109

Anuar Zhanatovich Zhunusov, Surgeon, Head of the Department of Fetal Cell Transplantation, JSC National Scientific Medical Center, Astana, Kazakhstan, dr.anuar.zhunussov@mail.ru, https://orcid.org/0009-0008 4188-8700.

Aigerim Khairullaevna Zhakupova, Biotechnologist of the Laboratory of Cellular Immunotherapy, JSC National Scientific Medical Center, Astana, Kazakhstan, s.aigerim.87@mail.ru, https://orcid.org/0009-0007 2042-0036.

Olga Vladimirovna Ulyanova, MD, PhD, Endocrinologist, JSC National Scientific Medical Center, Astana, Kazakhstan, olgaulyanova1971@gmail.com, https://orcid.org/0000-0002-7471-0633.

Larisa Vladimirovna Kozina, MD, PhD, Head of the Central Research Laboratory, JSC National Scientific Medical Center, Astana, Kazakhstan, l.kozina@nnmc.kz, https://orcid.org/0009-0004-3685-1998. ВЕСТНИК КАЗНМУ №4 (74) – 2025 ISSN 2524 – 0684 e-ISSN 2524 – 0692

@Fakhradiyev Ildar Rafisovich, MD, PhD, Vice-Rector at S.D. Asfendiyarov Kazakh National Medical University, fakhradiyev.i@kaznmu.kz, https://orcid.org/0000-0003-0528-3874.

Авторлар туралы мәліметтер

Ганина Анастасия Михайловна, биотехнолог, «Ұлттық ғылыми медициналық орталық» АҚ жасушалық технологиялар трансплантациялар бөлімінің меңгерушісі, anastassiya_smelova@mail.ru, https://orcid.org/0000-0002-2047-1497. Астана, Қазақстан

Ахаева Айжан Әбдісадыққызы, биотехнолог, б.ғ.к., «Ұлттық ғылыми медициналық орталық» АҚ жасушалық иммунотерапия зертханасының меңгерушісі, Астана, Қазақстан, akhaeva@mail.ru, https://orcid.org/0009-0007-4741-610

Жунусов Ануар Жанатұлы, хирург, «Ұлттық ғылыми медициналық орталық» АҚ фетальды жасушалар трансплантациясы бөлімінің жетекшісі, https://orcid.org/0009-0008-4188-8700 Астана, Қазақстан, dr.anuar.zhunussov@mail.ru

Жакупова Айгерім Хайруллақызы, жасушалық иммунотерапия зертханасының биотехнологы, «Ұлттық ғылыми медициналық орталық» АҚ, Астана, Қазақстан, s.aigerim.87@mail.ru, https://orcid.org/0009 0007-2042-0036

ISSN 2524 – 0684 **e-ISSN 2524 – 0692**

Ульянова Ольга Владимировна, м.ғ.к., «Ұлттық ғылыми медициналық орталық» АҚ эндокринолог дәрігері, Астана, Қазақстан, olgaulyanova1971@gmail.com, https://orcid.org/0000-0002-7471-0633

Козина Лариса Владимировна, м.ғ.к., «Ұлттық ғылыми медициналық орталық» АҚ Орталық ғылыми зерттеу зертханасының меңгерушісі, Астана, Қазақстан, l.kozina@nnmc.kz, https://orcid.org/0009-0004 3685-1998.

@Фахрадиев Ильдар Рафисович, MD, PhD, проректор, С.Ж. Асфендияров атындағы Қазақ ұлттық медицина университеті, fakhradiyev.i@kaznmu.kz, https://orcid.org/0000-0003-0528-3874.

Сведения об авторах

Ганина Анастасия Михайловна, биотехнолог, Руководитель отдела клеточных технологий и трансплантаций, АО «Национальный научный медицинский центр», Астана, Казахстан, anastassiya_smelova@mail.ru, https://orcid.org/0000-0002-2047-1497

Ахаева Айжан Абдисадиковна, биотехнолог, к.б.н., Руководитель лаборатории клеточной иммунотерапии, АО «Национальный научный медицинский центр», Астана, Казахстан, akhaeva@mail.ru, https://orcid.org/0009-0007-4741-6109

Жунусов Ануар Жанатович, хирург, руководитель отдела трансплантации фетальных клеток АО «Национальный научный медицинский центр», Астана, Казахстан, dr.anuar.zhunussov@mail.ru, https://orcid.org/0009-0008-4188-8700

Жакупова Айгерим Хайруллаевна, биотехнолог лаборатории клеточной иммунотерапии, АО «Национальный научный медицинский центр», Астана, Казахстан, s.aigerim.87@mail.ru, https://orcid.org/0009-0007-2042-0036

Ульянова Ольга Владимировна, к.м.н., врач-эндокринолог АО «Национальный научный медицинский центр», Астана, Казахстан, olgaulyanova1971@gmail.com, https://orcid.org/0000-0002-7471-0633

Козина Лариса Владимировна, к.м.н., Руководитель центральной научно-исследовательской лаборатории АО «Национальный научный медицинский центр», Астана, Казахстан, l.kozina@nnmc.kz, https://orcid.org/0009-0004-3685-1998

@Фахрадиев Ильдар Рафисович, MD, PhD, проректор, Казахский национальный медицинский университет им. С.Д. Асфендиярова, fakhradiyev.i@kaznmu.kz, https://orcid.org/ 0000-0003-0528-3874.

1 ЖӘНЕ 2 ТИПТІ ҚАНТ ДИАБЕТІ КЕЗІНДЕГІ ПЕРИНАТАЛДЫ МЕЗЕНХИМАЛДЫ БАҒАНАЛЫ ЖАСУШАЛАР ЖӘНЕ ОЛАРДЫҢ ЖАСУШАСЫЗ ӨНІМДЕРІ: ЖҮЙЕЛІ ШОЛУ

А.М. ГАНИНА [1], А.Ә. АХАЕВА [1], А.Ж. ЖУНУСОВ [1], А.Х. ЖАКУПОВА [1], О.В. УЛЬЯНОВА [1], Л.В. КОЗИНА [1], И.Р.ФАХРАДИЕВ [2]

[1] «Ұлттық ғылыми медицина орталығы» АҚ, Астана, Қазақстан

[2] «С.Ж. Асфендияров атындағы Қазақ ұлттық медицина университеті» КеАҚ, Алматы, Қазақстан

ISSN 2524 – 0684 e-ISSN 2524 – 0692

Түйіндеме

Кіріспе. 1 және 2 типті қант диабеті (ҚД) аурушаңдық пен өлім-жітімнің жетекші себептерінің бірі болып қала береді, ал науқастардың едәуір бөлігі қазіргі заманауи фармакотерапия аясында да HbA1c-тың нысаналы деңгейлеріне жете алмайды. Перинаталды мезенхималды бағаналы жасушалар (МБЖ) және олардың жасушасыз туындылары айқын иммуномодуляциялық және трофикалық әсерлерге ие және диабет ағымын модификациялаудың болашағы зор тәсілі ретінде қарастырылуда.

Мақсаты. Перинаталды МБЖ қолданылған ҚД 1 және ҚД 2 кезіндегі клиникалық деректерді жүйелендіру және диабет пен оның асқынулары кезінде перинаталды МБЖ-ның жасушасыз өнімдері (экзосомалар, шағын жасушадан тыс везикулалар, секретом, кондицияланған орта) бойынша доклиникалық нәтижелерді қорыту.

Материалдар мен әдістер. Жүйелі шолу PRISMA 2020 ұсынымдарына сәйкес орындалды. Іздеу 2000 жылғы қаңтардан 2025 жылғы 3 қазанға дейінгі кезеңде негізгі халықаралық биомедициналық дерекқорларда тілдік шектеусіз жүргізілді. ҚД 1/ ҚД 2 бар науқастарға перинаталды МБЖ немесе олардың жасушасыз туындылары қолданылған және диабетке бағытталған нәтижелері бар клиникалық зерттеулер, сондай-ақ диабет модельдерінде перинаталды экзосомалар, жасушадан тыс везикулалар, секретом немесе кондицияланған орта пайдаланылған доклиникалық жұмыстар енгізілді.

Нәтижелер. Шолуға 14 зерттеу (6 клиникалық, 8 клиникаға дейінгі) енгізілді. Рандомизацияланған зерттеулердің мета-талдаулары перинаталды көздерді қоса алғанда, МБЖ-терапия HbA1c-ты шамамен 1 пайыздық пункте төмендететінін, инсулин дозасын азайтатынын және С-пептид деңгейін арттыратынын, бұл ретте ауыр жағымсыз құбылыстардың жиілігі өспейтінін көрсетті. ҚД 2 кезінде перинаталды МБЖ қолданылған клиникалық зерттеулер HbA1c-тың 1–3%-ға төмендеуін және инсулинге қажеттіліктің 30–50%-ға азаюын, сонымен қатар инсулинге резистенттілік көрсеткіштерінің жақсарғанын көрсетті. Доклиникалық жұмыстар перинаталды экзосомалар, шағын жасушадан тыс везикулалар және секретом инсулинге резистенттілікті жақсартатынын, β-жасушаларды қорғайтынын, диабеттік жаралардың жазылуын жеделдететінін және нефро-, ретинопротективтік әсер қамтамасыз ететінін көрсетті. Қант диабеті кезінде перинаталды жасушасыз өнімдерге арналған клиникалық зерттеулер іздеу сәтінде анықталған жоқ.

Қорытынды. Перинаталды МБЖ, ең алдымен UC-MSC, клиникалық зерттеулерде ҚД 1 және ҚД 2 кезінде гликемиялық бақылаудың орташа, бірақ клиникалық тұрғыдан мәнді жақсаруын қамтамасыз етеді және қысқа мерзімді қауіпсіздік профилі қолайлы. Перинаталды МБЖ-ның жасушасыз туындылары бойынша доклиникалық деректер паракриндік механизмдердің негізгі рөлін және стандартизацияланған жасушасыз препараттардың перспективалы екенін растайды, бұл рандомизацияланған клиникалық зерттеулерде қосымша растауды талап етеді.

Түйінді сөздер: 1 типті қант диабеті, 2 типті қант диабеті, мезенхималды бағаналы/стромалдық жасушалар, кіндік бауының мезенхималды бағаналы жасушалары, жасушадан тыс везикулалар, жасушалық-тіндік терапия.

ПЕРИНАТАЛЬНЫЕ МЕЗЕНХИМАЛЬНЫЕ СТВОЛОВЫЕ КЛЕТКИ И ИХ БЕСКЛЕТОЧНЫЕ ПРОИЗВОДНЫЕ ПРИ САХАРНОМ ДИАБЕТЕ 1 И 2 ТИПА: СИСТЕМАТИЧЕСКИЙ ОБЗОР

ISSN 2524 – 0684 **e-ISSN 2524 – 0692**

А.М. ГАНИНА [1], А.Ә. АХАЕВА [1], А.Ж. ЖУНУСОВ [1], А.Х. ЖАКУПОВА [1], О.В. УЛЬЯНОВА [1], Л.В. КОЗИНА [1], И.Р.ФАХРАДИЕВ [2]

[1] АО «Национальный научный медицинский центр», Астана, Казахстан
[2] НАО «Казахский национальный медицинский университет имени С.Д. Асфендиярова», Алматы, Казахстан

Аннотация

Введение. Сахарный диабет 1 и 2 типа остается одной из ведущих причин заболеваемости и смертности, а значительная часть пациентов не достигает целевых уровней HbA1c даже на фоне современной фармакотерапии. Перинатальные мезенхимальные стромальные клетки (МСК) и их бесклеточные производные обладают выраженными иммуномодулирующими и трофическими эффектами и рассматриваются как перспективный подход к модификации течения диабета.

Цель. Систематизировать клинические данные по применению перинатальных МСК при СД1 и СД2 и обобщить доклинические результаты по перинатальным бесклеточным продуктам МСК (экзосомы, малые внеклеточные везикулы, секретом, кондиционированная среда) при диабете и его осложнениях.

Материалы и методы. Систематический обзор выполнен в соответствии с рекомендациями PRISMA 2020. Поиск проводили в основных международных биомедицинских базах данных за период с января 2000 г. по 3 октября 2025 г. без языковых ограничений. Включали клинические исследования СД1/СД2 с применением перинатальных МСК или их бесклеточных производных и диабет-ориентированными исходами, а также доклинические работы на моделях диабета с использованием перинатальных экзосом, внеклеточных везикул, секретома или кондиционированной среды.

Результаты. В обзор включено 14 исследований (6 клинических, 8 доклинических). Мета-анализы рандомизированных исследований показали, что МСК-терапия, включая перинатальные источники, снижает HbA1c на ~1 процентный пункт, уменьшает дозу инсулина и повышает С-пептид без увеличения частоты серьезных нежелательных явлений. Клинические исследования перинатальных МСК при СД2 демонстрируют снижение HbA1c на 1–3% и уменьшение потребности в инсулине на 30–50% с одновременным улучшением показателей инсулинорезистентности. Доклинические работы показали, что перинатальные экзосомы, малые внеклеточные везикулы и секретом улучшают инсулинорезистентность, защищают β-клетки, ускоряют заживление диабетических ран и обеспечивают нефро- и ретинопротективный эффект. Клинических исследований перинатальных бесклеточных продуктов при СД на момент поиска не выявлено.

Заключение. Перинатальные МСК, прежде всего UC-MSC, в клинических исследованиях обеспечивают умеренное, но клинически значимое улучшение гликемического контроля при СД1 и СД2 при благоприятной краткосрочной безопасности. Доклинические данные по перинатальным бесклеточным производным подтверждают ключевую роль паракринных механизмов и перспективность стандартизованных бесклеточных препаратов, что требует подтверждения в рандомизированных клинических исследованиях.

ISSN 2524 – 0684 **e-ISSN 2524 – 0692**

Ключевые слова: сахарный диабет 1 типа; сахарный диабет 2 типа; мезенхимальные стволовые/стромальные клетки; пуповинные мезенхимальные стволовые клетки; внеклеточные везикулы; клеточно-тканевая терапия.