KAMIŃSKA, Monika, JASIEWICZ, Maria, MIERNIK-SKRZYPCZAK, Magdalena, SPYRA, Aleksandra, MALICKA, Marta, DĄBROWSKA, Natalia, KOZIOŁ, Aleksandra and MOCZYRÓG, Katarzyna. The importance of stem cells in the treatment of type 1 diabetes, type 2 diabetes and diabetes complications: The importance of stem cells in diabetology. Quality in Sport. 2025;37:57420. eISSN 2450-3118.
https://doi.org/10.12775/QS.2025.37.57420
https://apcz.umk.pl/QS/article/view/57420

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 30.12.2024. Revised: 03.01.2025. Accepted: 03.01.2025 Published: 14.01.2025.

The importance of stem cells in the treatment of type 1 diabetes, type 2 diabetes and diabetes complications

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ABSTRACT

Introduction and Purpose. Diabetes, characterized by hyperglycemia due to impaired insulin production or action, leads to significant complications like diabetic retinopathy (DR) and diabetic foot syndrome (DFS). Current treatments manage symptoms but do not fully address disease progression. Stem cells, with their regenerative potential and immunomodulatory properties, represent a promising avenue for treating diabetes and its complications. This study explores the use of stem cell therapy in managing type 1 and type 2 diabetes, DR, and DFS.

Material and Method. The study reviewed existing literature on the application of stem cells in diabetes treatment. More than 30 articles addressing these issues were analyzed. They were found using the PubMed search engine, and the time frame of these publications covered the last 20 years.

Results. Stem cells demonstrated significant potential in diabetes management. For type 1 diabetes, MSCs reduced inflammation, preserved pancreatic islet function, and decreased insulin requirements without major adverse effects. Pluripotent stem cells showed promise in islet transplantation, achieving stable glycemic control in clinical trials. In type 2 diabetes, stem cell therapy improved insulin sensitivity and reduced insulin dependency, with evidence of β-cell regeneration. Complications like diabetic foot ulcers and retinopathy also responded positively to stem cell treatments. MSCs improved wound healing by enhancing tissue regeneration and reducing inflammation, while retinal therapies showed promise in slowing disease progression and repairing damaged vasculature.

Conclusions. Stem cell therapies offer a promising approach for diabetes and its complications, particularly for regenerative applications in DR and DFS. While initial results are encouraging, further large-scale studies are needed to optimize protocols, assess long-term safety, and establish standardized clinical applications.

Keywords: stem cells; type 1 diabetes mellitus; type 2 diabetes mellitus; diabetic wound healing; diabetic retinopathy

INTRODUCTION

Stem cells have the ability to potentially unlimited number of proliferations and differentiation into numerous cell types, and their origin can be somatic and embryonic [1]. The methods of obtaining them are different, because their source is mainly adipose tissue, bone marrow, cord blood and peripheral blood [1]. They have properties that are used, among others, in dermatology (e.g. ulcers, wounds, tissue regeneration), immunology (e.g. autoimmune diseases, because they affect the immune system) and ophthalmology (e.g. age-related macular degeneration, retinopathy) [1].

Diabetes is a group of metabolic diseases characterized by hyperglycemia, which is the result of impaired insulin production or action, and its most well-known types are type 1 diabetes and type 2 diabetes [2, 3]. Type 1 diabetes is an autoimmune disease (beta cells in the islets of the pancreas are damaged), and the autoantibodies contributing to its progression include: anti-zinc, anti-tyrosine phosphatases, anti-glutamic acid decarboxylase, anti-insulin and anti-islet [3]. Type 2 diabetes is characterized by hyperglycemia, insulin resistance and relative insulin deficiency, and obesity predisposes to its occurrence [2, 3]. The methods of treating diabetes include: lifestyle modification (physical activity and appropriate diet), insulin and non-insulin drugs (such as metformin, flozins and incretin drugs), and the properties of stem cells (their effect on the immune system and the ability to differentiate into many cell types) could be used in the treatment of diabetes [1, 3, 4]. An important issue is also the treatment of the implications of diabetes, which include microangiopathy (leading to damage to the eye, neuropathy and kidneys) and macroangiopathy (which increases the risk of stroke, ischemic heart disease and diabetic foot syndrome) [2, 3, 5]. Retinopathy is a disease process affecting the retina, which includes diabetic retinopathy, which is a result of damage to the blood vessels of the retina as a result of hyperglycemia and hypertension [3, 6]. Diabetic maculopathy (causing blockage of blood circulation in the retina) predisposes to its occurrence, and methods of treatment include vitrectomy, retinal laser photocoagulation, pharmacological treatment (such as antiplatelet drugs), and the properties of stem cells (impact on the immune system and tissue regeneration) could be used as a therapy for diabetic retinopathy [1, 3, 6]. Diabetic foot syndrome can have a neuropathic basis (which manifests itself in paresthesia and decreased sensation) and ischemic (resulting from damage to blood vessels), which can lead to deformation, ulcers and amputations [5]. Treatment includes pharmacological treatment, rehabilitation and surgical procedures, and the regenerative abilities of stem cells could be used to treat this complication of diabetes [1, 3, 5]. This paper will discuss the use of stem cells in the treatment of diabetes and its complications, with particular emphasis on diabetic retinopathy and diabetic foot syndrome.

TYPE 1 DIABETES MELLITUS

A 2024 meta-analysis of 13 studies on the treatment of diabetes with mesenchymal stem cells (MSCs) found that MSCs transplantation has a positive effect on patients with type 2 and type 1 diabetes (T1D). Those treated with MSCs had lower insulin requirements, as well as lower glycated hemoglobin (HbA1c), fasting blood glucose, fasting plasma glucose, and higher C-peptide levels. No significant adverse events were reported [7]. In their study, Zhou et al. investigated the effect of MSCs on T cell migration to pancreatic islets using a T1D mouse model. In both healthy and T1D mice, a significant increase in miR-25 levels in the peripheral circulation was observed after MSCs injection - miR-25 was highly expressed in MSCs exosomes. miR-25 caused the inhibition of the expression of the chemokine CXCR3, reducing the number of T cells and hindering their infiltration into the pancreas [8]. Utami et al. observed that the use of hypoxic secretome MSCs (HS-MSCs) in rats with T1D resulted in the regulation of superoxide dismutase (SOD) gene expression and inhibition of interleukin 6 secretion. The obtained results indicate the anti-inflammatory effect of HS-MSCs on pancreatic cells [9].
According to the study by Mićanović et al., mouse MSCs from hair follicles (moMSCORS) showed potential in preventing T1D.

In mice with induced T1D, moMSCORS administration reduced pancreatic islets inflammation and maintained insulin production. This effect was mainly mediated by inhibition of CD4+ T cell proliferation and activation [10]. Khalil et al. used MSC exosomes loaded with selenium or nano-selenium (NSe) to treat T1D in rats. Injection of these exosomes resulted in marked control of blood glucose levels. Administration of NSe-loaded exosomes caused even better anti-inflammatory effects on the pancreas, which translated into better control of glycemic control [11].

Jawale et al. treated 25 patients with T1D with autologous intrapancreatic stem cell therapy for 5 years. The results of this study were compared with individuals in a control group treated with insulin. Patients treated with MSCs achieved greater weight gain, higher C-peptide levels, and lower daily insulin requirements, glutamic acid decarboxylase antibody levels, and HbA1c levels, as well as fasting and postprandial blood sugar levels. Only minor adverse effects were observed during therapy. The authors also suggested that intrapancreatic infusion of MSCs into the pancreas via the pancreatic artery allows for higher MSCs concentrations and thus better therapeutic effects compared with intravenous administration [12]. In a retrospective cohort study, Leão et al. analyzed 7 patients who received an infusion of adipose-derived MSCs (AMSCs) within 3 months of T1D diagnosis, and supplementation with 2000 IU cholecalciferol for 1 year, starting the day after the infusion. Patients treated with AMSCs and vitamin D showed a higher rate of partial clinical remission and lower total daily insulin requirements compared to the control group [13].

Pluripotent stem cells (PSCs) can be used for islets of Langerhans transplantation. Wang et al. in October 2024 presented 1-year results from one patient as a preliminary analysis of a first-in-human phase I clinical trial evaluating the feasibility of autologous islets transplantation derived from chemically induced PSCs (CiPSC islets) under the abdominal anterior rectus sheath for the treatment of T1D. The target glycemic range (96.21%) was achieved by month 4 after transplantation. A decrease in HbA1c level was observed. After this time, the patient achieved a state of stable glycemic control (>98%). Sustained insulin independence was maintained from day 75 after transplantation [14]. This study has significantly contributed to the introduction of novel therapeutic options for patients diagnosed with T1D.

TYPE 2 DIABETES MELLITUS

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder that develops resulting from progressive disturbances in glucose homeostasis. It is characterized by impaired glucose control resulting from reduced insulin sensitivity (insulin resistance) and dysfunction in insulin secretion due to the progressive pancreatic β-cell dysfunction responsible for its production. As a result of these pathological processes, there is a deterioration in blood glucose control, leading to hyperglycemia and subsequent metabolic complications such as nephropathy, retinopathy, and neuropathy [3, 15, 16, 17, 18]. Type 2 diabetes is the most common form, accounting for about 90–95% of diabetes cases. It is considered a significant health problem among the elderly and is currently regarded as one of the main causes of mortality in populations over the age of 60 [16]. The prevalence of T2DM is steadily increasing, likely due to socio-economic development, lifestyle changes, and an aging population [3].

The cornerstone of T2DM therapy involves maintaining normal blood glucose levels through the use of medications that enhance tissue insulin sensitivity or stimulate β-cell secretory activity. However, the use of exogenous insulin therapy, despite its efficacy in controlling glucose levels, is associated with weight gain, hypoglycemia risk, hepatic damage, and an inability to replicate the physiological rhythm of insulin secretion [15 ,17]. Apart from pharmacological therapy, individualized non-pharmacological strategies are recommended, which include lipid profile regulation, body weight control, and lifestyle modification. These interventions may improve glycemic control in the short term but are not sufficient to halt disease progression or significantly reducing type 2 diabetes morbidity rates [3, 17, 18]. Consequently, there is an increasing demand for modern therapies directly targeting β-cell function, their regeneration, and the induction of neogenesis of new β-cells. Such approaches could represent a crucial element in more effective T2DM management and in limiting its long-term complications [3, 15, 17, 18].

In recent years, the number of studies investigating the use of stem cells in treating T2DM and its complications has expanded significantly. Both clinical trials and experiments on animal models provide more evidence supporting the therapeutic potential of mesenchymal stem cells (MSCs) in tissue regeneration and the enhancement of metabolic functions [18]. An example of this is a prospective study conducted from 2015 to 2018 by Zang L., Li Y., Hao H., and colleagues, evaluating the efficacy and safety of using umbilical cord-derived mesenchymal stem cells (UC-MSCs) in patients with T2DM. The study involved 91 Chinese adults with T2DM diagnosed for less than 20 years. Eligibility criteria included inadequate glycemic control despite insulin therapy for at least 3 months, fasting C-peptide levels ≥ 1 ng/ml, and a body mass index (BMI) between 24–40. Participants were randomized into two groups: one receiving UC-MSCs intravenously and the other receiving a placebo. The treatment or placebo was administered three times over a four-week period, followed by a 48-week observation phase. Blood glucose levels (HbA1c) and daily insulin requirements were measured every 12 weeks. Additionally, β-cell function was assessed after 9, 20, and 48 weeks. After 48 weeks, 20% of patients in the MSC group reached the target HbA1c < 7.0% and daily insulin reduction ≥ 50%, compared to only 4.55% in the placebo group. Furthermore, 13.5% of patients receiving stem cell therapy completely discontinued insulin use within 8 to 24 weeks, while no patients in the placebo group managed to cease insulin therapy. Although the study demonstrated significant improvements in glycemic control and insulin dependency in the treatment group, it did not show substantial enhancements in β-cell function in patients with T2DM [15].

In another study conducted by Guan L., Guan H., Li H., and colleagues, the safety and efficacy of stem cell therapy were assessed in six T2DM patients. The participants received two intravenous infusions of stem cells two weeks apart, followed by at least 24 months of observation. Blood glucose levels were monitored daily for the first three months, and then weekly for the following three months. Exogenous insulin requirements were determined based on fasting plasma glucose levels. Additionally, C-peptide, HbA1c levels, and pancreatic autoantibodies (GAD-Ab, ICA, and IAA) were assessed. Patients were also closely monitored for any adverse effects throughout the study. During the first three months, 50% of patients were completely insulin-free from 25 to 43 months. For the remaining patients, lower doses of insulin were still required.

In the group needing insulin, C-peptide levels significantly increased after the first month, then decreased after the third month. In contrast, patients who did not require insulin saw a steady increase in C-peptide levels, suggesting an improvement in pancreatic β-cell function. No adverse effects were reported among the participants receiving stem cell infusions [16]. A prospective, randomized study by Bhansali A., Asokumar P., Walia R., and colleagues evaluated the efficacy and safety of autologous bone marrow-derived mesenchymal stem cell transplants (ABMSCT) in T2DM patients. Twenty-one patients aged 30 to 70 were included based on the following criteria: T2DM for ≥5 years, failure of triple antidiabetic therapy, insulin bolus requirements ≥0.4 IU/kg body weight per day, and HbA1c <7.5%. Participants were randomly assigned to receive either stem cell therapy from bone marrow or placebo. Patients received two doses of the treatment or placebo, followed by 12 months of observation. Nine out of eleven patients receiving ABMSCT showed a reduction in insulin requirements of over 50% relative to baseline while maintaining HbA1c <7%. None of the placebo recipients achieved this result during the study period. After 12 months, insulin requirement reduction was 66.7% in the treatment group compared to 32.1% in the placebo group. Among those receiving stem cells, C-peptide levels significantly increased, which was not observed in the placebo group. No significant changes in HOMA-IR and HOMA-β were observed in either group, and there were no adverse effects associated with the therapy [17].

Scientific studies suggest that the intravenous administration of stem cells represents a promising and potentially safe therapeutic approach for patients with type 2 diabetes mellitus (T2DM). This method has been associated with reduced requirements for exogenous insulin and improved insulin sensitivity [15, 17]. The findings highlight the potential efficacy and safety of this method, suggesting the possibility of utilizing stem cell transplants as a modern therapeutic strategy in treating T2DM [15, 16, 18]. However, researchers believe that the efficacy of stem cell therapy may depend on factors such as the duration of diabetes, the number of preserved functional β-cells, and the tissue microenvironment conditions [16]. Consequently, further well-designed clinical trials with larger patient numbers are needed to precisely determine the efficacy and safety profile of intravenous administration of mesenchymal stem cells derived from umbilical cords (UC-MSCs) in treating T2DM [15, 16, 17, 18].

DIABETIC WOUND HEALING

Development of ulceration in patients with diabetes is very common, according to Verdi J et. all. even 15% of patients with this disease will develop diabetic foot ulcers (DFU), as reported by Amstrong et. all. 18.6 million people will develop DFU and more than half of them will be the source of the infection that can lead to amputation of the lower extremities [19, 20]. Blood vessel disease, peripheral neuropathy and wound infections influence development of diabetic foot ulceration. That condition comes with a 2.5 times increased 5-year risk of death. Because of the pathological environment that leads to oxygen deprivation, reduced blood flow to tissues and elevated glucose levels, typical stages of wound healing are disrupted [21].

Stem cells have an impressive impact on improving rejuvenation of vessels, synthesizing activation of growing factors and limiting the amount of inflammatory factors [22]. A variety of stem cell origin that is used for wounds: embryonic mesenchymal stem cells, bone marrow mesenchymal stem cells, adipose stem cells, umbilical cord mesenchymal stem cells.

Unique representations of stem cells are bone marrow mesenchymal cells, because they provide hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs).
According to Gupta et. all they have the capacity to activate the process of differentiation of the resident progenitor cells [23]. They maintain an essential feature which is an opportunity to convert into different types of cells, such as cartilage, muscle, connective tissue, and adipose. They can be administered topically or as an injection. Considerable advantage of this therapy is that just after 2 weeks there is noticeable improvement in wound healing, taking into account wound size, enhanced number of vessels and density of tissue that is surrounding wounds [24]. There are positive outcomes reported of stem cells originating from adipose tissue that improve wound healing, increasing the quantity of skin keratinocytes and fibroblast growth factors such as GDF11, TGF-β, b-FGF, VEGF, TLR2, TLR4, IL-10, and MMP which are engaged in cell proliferation [25, 26]. To improve this model of therapy there is evidence supporting the importance of stem cells implantation to specific platforms that help with their preservation and can be a base from which stem cells can be portioned [27]. According to studies ADSCs improve wound healing by stimulating paracrine activity through chemokines mentioned above [28].
Studies carried out about umbilical cord mesenchymal stem cells likewise show improvement in wound healing, by way of minimizing area, length and width of lesions [29]. However there should be more studies conducted with an increased sample size.
Although Sun et. all. meta-analysis conducted that stem cells don't have an impact on increasing the blood flow to ulcerations, however their usage results in a decreased amount of amputations of lower limbs [30].

DIABETIC RETINOPATHY

Diabetic retinopathy (DR) is one of the most common causes of vision loss in developed countries, resulting from chronic hyperglycemia associated with both type 1 and type 2 diabetes. This condition affects the blood vessels in the retina, where prolonged high blood glucose levels lead to damage to the vessel walls, ruptures, and consequently to hemorrhages, edema, and the formation of new, abnormal blood vessels. The progression of diabetic retinopathy can lead to deteriorating vision, and in severe cases, total blindness.
The treatment of diabetic retinopathy is multifaceted and depends on the stage of the disease. In its early stages, where the changes are still reversible, controlling blood sugar levels, blood pressure, and lipids is crucial. In more advanced stages, where complications such as macular edema or hemorrhages are present, pharmacological treatments (anti-VEGF injections) and procedures, such as laser photocoagulation, are used. In the most severe cases, when other methods fail, surgical interventions like vitrectomy may be considered. The modern approach to treating diabetic retinopathy emphasizes early detection and comprehensive therapy, aimed at halting disease progression and preventing vision loss [31].
The current treatments for diabetic retinopathy only delay or prevent the progression of the disease, and research on its pathogenesis and etiology remains limited. Many studies have confirmed that stem cells play a role in the development of diabetic retinopathy, and the mechanisms underlying this relationship are still being investigated.
Stem cells have the potential to slow the progression of diabetic retinopathy and alleviate its symptoms.

Stem cells can secrete growth factors that have neuroprotective effects, or reduce and repair capillary congestion, protecting damaged blood vessels. Recent experimental animal studies have confirmed the effectiveness of regenerative therapies in treating this disease. Various types of cells have been used in these studies, including endogenous cells, endothelial progenitor cells, embryonic stem cells, induced pluripotent stem cells, and mesenchymal stem cells. There has been particular interest in therapies based on mesenchymal stem cells, endothelial progenitor cells, and adipose stromal cells, which have shown promising results in preventing damage and supporting retinal regeneration [6].

Mesenchymal stem cells: Research suggests that mesenchymal stem cells could be a promising therapeutic option; however, their clinical application in the treatment of diabetic retinopathy remains controversial and requires further clinical studies to fully assess their potential.

Endothelial progenitor cells: These cells demonstrate greater resistance to oxidative stress compared to mature endothelial cells, which may be important in the treatment of diabetic retinopathy, particularly in preventing damage to retinal blood vessels.

Adipose-derived stem cells: These cells may help lower blood glucose levels and play a role in neurovascular protection. However, their direct impact on improving the retinal microenvironment and conditions within the retina is still not fully understood.

Pluripotent stem cells: Pluripotent stem cells have the ability to differentiate into various types of mature cells, making them a promising option for treating retinopathy. Induced pluripotent stem cells, particularly in animal models, show potential for improving visual acuity, paving the way for future therapies [6].

In recent years, an increasing number of clinical studies have focused on the use of mesenchymal stem cells in the treatment of diabetic retinopathy and other eye diseases. Several therapeutic approaches are being explored, including the transplantation of pluripotent stem cells and induced pluripotent stem cells, which exhibit characteristics similar to photoreceptor cells and retinal pigment epithelium.Some clinical trials also involve cells derived from adipose tissue and bone marrow, which are transplanted into the eye to regenerate damaged retinal tissue [32].

Stem cell therapy shows significant potential. Recent studies have shown that autologous bone marrow-derived stem cells led to significant improvements in patients with non-proliferative diabetic retinopathy (NPDR), improving macular thickness and visual acuity. These findings suggest that MSCs could be an effective therapeutic option for treating DR, although further clinical trials are needed to determine the optimal treatment methods and ensure their safety [32].

Recent studies show that activation of the NLRP3 inflammasome plays a key role in the progression of diabetic retinopathy. Increased levels of inflammasome components and pro-inflammatory factors have been detected in the retinas of diabetic models as well as in the vitreous body of DR patients. Intravitreal injection of mesenchymal stem cell-derived small extracellular vesicles (MSC-sEVs) significantly reduced the activation of the NLRP3 inflammasome and lowered the production of inflammatory factors. This treatment also improved the retinal condition, as evidenced by better retinal structure and function.

Diabetic conditions lead to inflammation in the retinal vessels, increasing their permeability and damaging the blood-retinal barrier. In line with previous studies, MSC-sEV injection reduced vessel leakage and helped restore the integrity of the retinal barrier.

These findings highlight the potential of MSC-sEVs as a promising therapy for diabetic retinopathy, suggesting that their beneficial effects may be due to inflammation reduction and retinal cell protection [33].

CONCLUSIONS

Diabetes is becoming a significant health problem and one of the main causes of mortality among individuals over the age of 60 [16]. There's a huge need for research on prevention and treating both the disease and its complications which include microangiopathy, macroangiopathy. Those complications implement further health problems [2, 3, 5, 6, 15, 16, 17, 18]. Retinopathy affects the retina by damaging its blood vessels due to hyperglycemia and hypertension [1, 3, 6, 31]. Ischemia and neuropathy can result in diabetic foot syndrome that leads to deformation, ulcers and eventually amputation [2, 3, 5, 21]. Treatment of those afflictions includes pharmacotherapy as well as changing lifestyle, implementing proper diet, rehabilitation and surgical procedures [1, 3, 5]. According to new research the stem cell could also be helpful in the treatment of not only diabetes but also its complications.

Stem cells are able to proliferate numerously and differentiate into various types of cells. There are multiple ways of obtaining them since there are few sources of them in the human body. They are widely used in different branches of medicine and a wide range of medical procedures [1].

When it comes to treating Type 1 Diabetes Mellitus, some promising studies have been conducted. According to those researches, patients treated with mesenchymal stem cells (MSCs) required less insulin, had lower glucose levels in blood tests and higher C-peptide levels. Additionally the results indicated anti-inflammatory effects of MSCs on pancreas [7, 8, 9, 10, 11, 12, 13]. Transplantation of pluripotent stem cells in the patient suffering from DM type 1 has shown that PSCs can also be used in treatment of this disease - 4 months after the procedure the target glycemic range and a state of stable glycemic control were achieved [14]. Moreover, no or only minor, insignificant adverse effects were reported during those studies [7, 10, 11, 12, 13, 14].

Similar studies have been conducted on patients with DM type 2. Mesenchymal stem cells were administered intravenously in patients which resulted in lower glycated haemoglobin levels, daily insulin reduction and overall better glycemic control [15, 16, 17]. Intravenous administration of stem cells has a potential to become a safe and effective therapy for patients with T2DM since there were no adverse outcomes [15, 16, 18].

Stem cells promote vessel rejuvenation by activating growing factors and reducing inflammatory factors [22]. Bone marrow stem cells deserve special attention since they provide hematopoietic and mesenchymal stem cells. They have an unique ability to convert into different types of cells and influence wounds healing by promoting proliferation of the cells, decreasing the wound size, increasing number of vessels and density of surrounding tissue [24, 25, 26, 27, 28, 29].

Recent studies show that there's a huge potential for using stem cells as a diabetic retinopathy treatment. Current treatment options only delay the progression of the disease but don't treat it. Wide range of stem cells provide various therapeutic options - they prevent vessel damage, have neuroprotective abilities and are resistant to oxidative stress [6].

Although the studies look promising for the future and provide much evidence on the positive effect of stem cells during the treatment of DM and its implications, their working is yet to be established. There's a huge need for further research in order to determine the optimal treatment methods and ensure their safety [6, 32, 33].

Disclosure:
Authors' contributions:
- conceptualization: M Kamińska
- methodology: M Kamińska
- software: Not applicable
- check: K Moczyróg
- formal analysis: K Moczyróg
- investigation: M Kamińska, M Jasiewicz, A Sierpińska, A Spyra, M Malicka, N Dąbrowska, A Kozioł
- resources: Not applicable
- data curation: M Kamińska, M Jasiewicz, A Sierpińska, A Spyra, M Malicka, N Dąbrowska, A Kozioł
- writing: M Kamińska, M Jasiewicz, A Sierpińska, A Spyra, M Malicka, N Dąbrowska, A Kozioł
- rough preparation: M Kamińska, M Jasiewicz, A Sierpińska, A Spyra, M Malicka, N Dąbrowska, A Kozioł, K Moczyróg
- visualisation: Not applicable.
- supervision: K Moczyróg
- project administration: M Kamińska, M Jasiewicz, A Sierpińska, A Spyra, M Malicka, N Dąbrowska, A Kozioł, K Moczyróg
- receiving funding: Not applicable

All authors have read and agreed with the published version of the manuscript.

FUNDING STATEMENT: The study received no specific funding.

INSTITUTIONAL REVIEW BOARD STATEMENT: Not applicable – Not required.

INFORMED CONSENT STATEMENT: Not applicable – Not required.

DATA AVAILABILITY STATEMENT: Not applicable.

CONFLICTS OF INTERESTS: The authors deny any conflict of interest.

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