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The use of stem cells in the treatment of diabetes mellitus and its complications - review

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ABSTRACT

Introduction and purpose

Diabetes is a disease resulting from impaired action or secretion of insulin. The number of patients currently amounts to approximately 422 million, and approximately 1.5 million deaths per year are directly attributed to this disease. Diabetes significantly reduces the quality of life and, if poorly controlled, can lead to serious complications. Mesenchymal stem cells are multipotent cells capable of differentiation. They have the ability to self-renew and have a modulating function. There are reports that they can be used in the treatment of this disease. The aim of the review was to present a new method of therapy and their possible effects.

Material and methods

The review was based on articles obtained from PubMed scientific database in the years 2015-2023, using the following keywords: diabetes mellitus, stem cells, diabetes complications.

Results

Implanted stem cells are able to transform into cells that produce and secrete insulin, and also enable better glycemic control. They can alleviate chronic inflammation and reduce fibrosis. Taking into account the complications that occur during long-term diabetes, the use of stem cells may be associated with improving the function of specific organs and tissues such as the kidneys, heart, eyes and nerves. Studies also report a positive effect of these cells on the healing process of wounds and ulcers.

Conclusions

Stem cells are a promising object of analysis. They can control glycemia and have a positive effect on the functioning of the kidneys, heart, eyes and nerves, and accelerate wound healing, but further, extensive research is needed to assess the effectiveness and safety of this therapy.

Keywords: diabetes mellitus; stem cells; diabetes complications.

Introduction

Diabetes is a chronic metabolic disease characterized by elevated blood glucose levels. The global incidence of this problem in adults increased from 4.7% in 1980 to 8.5% in 2014 [1], and the number of patients is currently approximately 422 million. Moreover, approximately 1.5 million deaths per year are directly attributed to this disease [2]. The most common forms include type 1 diabetes, in which insulin deficiency is caused by autoimmune destruction of pancreatic islet cells, and type 2 diabetes (approx. 80% of patients), which is characterized by insulin resistance leading to hyperglycemia [3,4]. Diabetes not only reduces the quality and length of life, but also in an insidious and chronic way leads to serious complications such as neuropathy, nephropathy, retinopathy, accelerated development of atherosclerosis and diabetic foot syndrome [5,6]. Pharmacological treatment of diabetes is most often based on a therapy consisting of several drugs, the basic of which is metformin [7]. However, the increasing number of patients, the number of complications and adverse effects of drugs mean that new treatment methods are constantly being sought. Mesenchymal stem cells are defined as non-hematopoietic multipotent cells capable of differentiating into the mesodermal, ectodermal and endodermal lineages. Moreover, they have excellent self-renewal ability and also have an immunomodulatory function [8]. There are reports that they can be used in the treatment of diabetes and alleviating the complications of this disease. The aim of the review was to present a new method of therapy and their possible effects.

Material and methods

The review was based on articles obtained from PubMed scientific database in the years 2015-2023, using the following keywords: diabetes mellitus, stem cells, diabetes complications.

Treatment of diabetes

Diabetes is a disease that damages many organs and tissues, therefore the therapy includes both pharmacological methods controlling the level of glycemia (oral drugs lowering the level of glycemia and insulin), combating factors increasing the cardiovascular risk (correcting lipid disorders and stabilizing blood pressure), as well as treating complications of this disease. In a study by M. El Sherbiny et al., rats with streptozotocin-induced diabetes were injected with mesenchymal stem cells (MSCs) from human umbilical cord and therapeutic response

was analyzed. In the group of animals that did not receive stem cells, the glucose level was 455.5 mg/dl at week 10, while in the group after MSC injection was 121.9 mg/dl, respectively. Additionally, liver sections were immunostained against human insulin during histological examination. In the group in which stem cells were not used, no expression of human insulin was detected, while in the group after MSC implantation in the liver, clusters of positively stained cells appeared around the veins of the central hepatic lobules. This means that MSCs were able to secrete insulin and partially control diabetes [9]. Another study used stem cells (MSCs) modified to overexpress FGF21 and GLP1. Then they were transplanted into mice with type 2 diabetes. It was found that MSC-GF21-GLP1 therapy resulted in inhibition of weight gain, lower blood glucose levels and a slight increase in insulin levels. This effect was superior compared to other treatment regimens (MSC, MSC-FGF21, MSC-GLP1). Moreover, a significant improvement in the lipid profile was noticed [10]. An interesting therapeutic option may be to replace damaged pancreatic islet cells by implanting stem cells. In a study involving 17 patients with type 1 diabetes, stem cells were differentiated into pancreatic endocrine cells and then implanted subcutaneously using a VC-02 macroencapsulation device. Insulin expression was observed in 63% of VC-02 removed from study participants during 3-12 months after implantation, while C-peptide was detected in 6 of 17 patients after 6 months. Unfortunately, despite the detection of C-peptide, no clinical benefit was noted, which was probably caused by too little implanted cells, therefore further optimization of the device and/or method of cell administration is necessary [11]. Another method of treating type 1 diabetes may be autologous mesenchymal stem cell transplantation, which was used in the study by Izadi et al. 21 patients diagnosed with type 1 diabetes aged 5 to 40 years were divided into 2 groups, one of which received 2 intravenous infusions of MSCs, and the second one - physiological saline infusion in weeks 0 and 3 of the study, respectively. During the one-year follow-up, it was determined that the incidence of grade I (glycemia 70-55) and grade II (55-40) hypoglycemia and the number of total hypoglycemic events decreased significantly in the study group, which was considered not only a safety parameter but also an effectiveness parameter. Due to MSCs, a reduction in the percentage of glycated hemoglobin, the concentration of pro-inflammatory cytokines (IL-6, TNF- α), and an increase in the concentration of anti-inflammatory cytokines (IL-4, IL-10) were achieved. A significant limitation of this therapy may be the time from diagnosis of diabetes to initiation of treatment, as patients who received an infusion in the first year after diagnosis had a significant decrease in the level of glycated hemoglobin and an increase in C-peptide levels compared to patients

whose treatment was started later [12]. In another study, which also involved a transplant, attention was focused on the analysis of the concentrations of antibodies characteristic of type 1 diabetes, i.e.: antibodies against insulin (AIA), antibodies against pancreatic islets (ICA), antibodies against glutamic acid decarboxylase (GAD) and antibodies against tyrosine phosphatase 2 (IA2). During the 6-month follow-up, 5 out of 6 patients included in the study showed the absence of ICA and a slow decline in GAD and IA2 values, while in all of them the AIA level remained at a high level [13].

In type 2 diabetes, insulin resistance leads to progressive dysfunction of pancreatic β cells, which is why there are studies involving patients that analyze whether stem cells can improve the functions of these cells and better control the disease. Lian et al. assessed the effectiveness of intravenous infusion of MSCs (1 infusion once a week for 3 weeks) based on parameters such as: fasting glucose, glycated hemoglobin, as well as the β -cell function index, insulin resistance index (HOMA-IR) and dosage of hypoglycemic drugs. On day 14 \pm 3 after administration of the first dose, an average decrease in fasting glucose concentration was observed from 9.34 mmol/l to 6.52 mmol/l, on day 84 \pm 3 there was a significant decrease in glycated hemoglobin from 7.80% to 7, 15%. Additionally, the β -cell function index increased from 29.90% to 40.97% around day 28, and HOMA-IR decreased, but not to statistically significant values. On day 84 \pm 3, all patients had their hypoglycemic drug dose reduced, and one patient discontinued the drugs completely [14].

In another study, in patients after 3 MSC infusions and 48 weeks of follow-up, a significant reduction in the daily insulin dose was found by 27.78% (placebo 15.62%) and a decrease in glycated hemoglobin concentration by 1.31% (placebo 0.68%). 20% of patients in the study group achieved the primary endpoint (HbA1c $<7\%$ and daily insulin dose reduction by $\geq 50\%$) compared to 4.55% in the placebo group [15].

The duration of type 2 diabetes, as in the case of type 1 diabetes, may affect the effectiveness of this method, as the study by Nguyen et al. showed a significant reduction in glycated hemoglobin in patients whose disease duration was shorter than 10 years. Moreover, no significant changes were found in the concentrations of HbA1c, fasting glucose and C-peptide in patients with a history of at least 10 years. Interestingly, body weight also had an impact on these parameters, as BMI less than 23 was associated with better results [16]. The use of MSC transplantation did not lead to the occurrence of serious side effects, which allows us to conclude that this therapy is safe [13,14,15,16]. However, it is necessary to conduct further

multicenter studies, especially on large groups of patients with different disease duration, to determine for which patient this therapy will be most appropriate.

Treatment of complications

Correct glycemia is a key element of diabetes control, but despite treatment, complications may occur, and the risk of their occurrence increases with the duration of the disease. These include: diabetic nephropathy, diabetic retinopathy, neuropathy, macrovascular complications and diabetic foot syndrome. Diabetic nephropathy (DN) is one of the most serious complications, and studies have shown that standard treatment controlling glycemia and blood pressure may not stop the progression of DN to end-stage renal disease [17], therefore it is important to intensively search for new effective methods of prevention. In a study by E. Xiang et al., human umbilical cord tissue stem cells (UC-MSC) were isolated and then injected into the tail vein of rats with streptozotocin-induced nephropathy. Compared to the control group, there was a significant improvement in renal parameters such as daily urine protein, creatinine clearance, and creatinine concentration in serum, urea level. Moreover, a reduced severity of pathological changes in the kidneys (vacuolar degeneration, inflammatory infiltration, interstitial fibrosis) and a reduction in the level of pro-inflammatory cytokines (IL-6, IL-1 β , TNF- α) in the blood of rats with diabetic nephropathy were observed [18]. Another study using stem cells derived from the urine of healthy men also found less loss of kidney function and reduced levels of fibrosis and inflammatory infiltrate in a mouse model with nephropathy compared to the control group [19]. Diabetic neuropathy is the most common complication of diabetes, which may affect up to 50% of patients over time. It causes pain, leads to an increased frequency of falls and reduces the quality of life [20]. In the course of hyperglycemia, glycation end products are formed, which damage the nerve (atrophy of nerve sheaths and direct damage to fibers). In the study by B. Fan et al., stem cells derived from mouse bone marrow were used and exosomes (nanovesicles of endosomal origin containing micro-RNA) were isolated from them. The control group consisted of animals without diabetes, and the research group with diabetes was divided into 2 subgroups (treated with saline and MSC exosomes). It was found that in the group treated with exosomes the motor nerve conduction velocity (MCV) increased by 16.8%

after 4 weeks of treatment and by 30.3% after 8 weeks of treatment, and the sensory nerve conduction velocity (SCV) by 17.3% and 24.9%. In addition, the same group examined the increased density of microcirculation in the sciatic nerves compared to mice treated with saline. Moreover, before treatment, a reduction in myelin area (MBP+) by 31.1% and axon area (NF200+) by 34.2% in individuals from the research group compared to the control group was determined. After stem cell treatment, the MBP+ area increased by 7.9% and the NF200+ area by 12.8%, which confirms a positive effect on axonal myelination [21].

The lifetime risk of developing a foot ulcer in a diabetic patient is estimated at 19-34%, and the recurrence rate is high (40% within a year of healing and 65% within 5 years) [22]. Moreover, the appearance of a foot ulcer is associated with a higher risk of lower limb amputation in the future [23]. The main risk factors are neuropathy and ischemia, but hyperglycemia also induces the formation of reactive oxygen species and impairs the function of endothelial progenitor cells, which may lead to the progression of this complication of diabetes [24]. To investigate whether stem cells have an impact on the healing of wounds and ulcers, a study was conducted in which wounds were created in anesthetized mice, which were then photographed, and the wound healing index was calculated based on statistical analysis. It was determined that the rate in animals with normoglycemia was $30 \pm 4.5\%$ on day 7 and $79 \pm 4.9\%$ on day 14, while in mice with type 1 diabetes it was reduced and amounted to $10 \pm 3.0\%$ and $34 \pm 5.0\%$. After injections of stem cells derived from adipose tissue, the index value increased to $20 \pm 3.2\%$ after 7 days and $70 \pm 3.8\%$ after 14 days, which shows that this therapy can accelerate wound healing [25].

In another study by J. Yang et al., exosomes isolated from human umbilical cord stem cells were used, which in combination with the Pluronic F-127 hydrogel were applied topically to a skin wound in a streptozotocin-induced diabetic rat model. Compared to the group treated with only exosomes or only hydrogel, the group treated with the combination of these methods showed the formation of new hair follicles in the center of the wound, subepidermal proliferation of fibroblasts, ordered and appropriate collagen deposition, as well as increased expression of the proliferation marker Ki67. Moreover, in the group treated with exosomes only and exosomes combined with hydrogel, higher activity of growth factors such as VEGF and TGF- β was demonstrated [26].

The study by Uzun et al. assessed the safety and effect of MSCs in patients with chronic diabetic foot ulcers. In the control group (10 patients) wound care was used, while in the research group (10 patients) wound care and stem cells were used. Wound closure was achieved in 17 patients (9 from the research group and 8 from the control group). A more

important parameter differentiating both groups turned out to be the time in which this was achieved, because in the research group this time was on average 31.0 ± 10.7 days, and in the control group 54.8 ± 15.0 days. Additionally, parameters such as general health and physical functioning assessed using special indicators showed higher values after MSC injections. The disadvantage of this method may be the cost of treatment, which was significantly higher in the research group. However, taking into account the shortening of the therapy time and the possibility of a faster return to everyday functioning and work, this may be more cost-effective in long term [27]. Diabetic retinopathy is one of the leading causes of vision loss and the number of patients with this problem continues to grow. Poor glycemic control and long duration of the disease promote vascular proliferation and the formation of macular edema, which leads to vision deterioration [28]. Therefore, it is important to find methods to delay the progression of the disease, especially at an early stage of development. In the study by L. Rong et al., CD 133+ stem cells were used, which were transplanted into the vitreous body of mice with streptozotocin-induced diabetes to analyze the visual function and structure of the retina. It was found that the stem cell transplant prevented visual dysfunction during the experiment. Histological analysis showed that CD 133+ migrated to the inner layers of the retina, causing the preservation of ganglion cells and bipolar rod cells. Moreover, stem cells expressed brain-derived neurotrophic factors (BDNF) in vivo and also increased BDNF levels in the diabetic retina, which has a positive effect on retinal cell survival [29]. Another study used CD 34+ stem cells, which are recruited from the bone marrow in the event of ischemia and play an important role in revascularization. After the injection of stem cells (research sample) and physiological saline (control sample), the density of retinal vessels was analyzed and it was found that in the control group the density was 11.41 ± 1.60 , while in the research group it was 13.39 ± 2.53 . Additionally, microarray analysis was performed and a change in the expression of 162 mouse retinal genes was demonstrated after intravitreal injection of CD 34+. The main changes concerned the pathways responsible for the pathogenesis of retinopathy, including Toll-like receptor, MAP kinase, oxidative stress, cellular development, organization and assembly pathways [30]. Excessive and inappropriate deposition of extracellular matrix is a complication occurring in patients with advanced, poorly controlled diabetes and may lead to dysfunction of organs such as the heart or liver. Hyperglycemia, lipotoxic damage, and insulin resistance activate fibroblasts and promote a fibrogenic phenotype in immune and vascular cells, leading to fibrosis [31]. Stem cell therapy may have a beneficial effect on the performance of damaged myocardium (increase in left

ventricular ejection fraction and increase in the diastolic function index) and inhibit fibrosis by reducing collagen deposition and TGF- β activity. This effect may be caused by the secretion of prostaglandin E2 with regulatory properties by stem cells [32]. In the study by S. Yu et al., a model of rats with long-term diabetes was created and the impact of mesenchymal stem cells (MSCs) on the condition of organs damaged in the course of the disease (lungs, heart, liver and kidneys) and chronic inflammation was analyzed. Quantification of gene expression showed that the number of tissue fibrosis markers (type I collagen, type III collagen, α smooth muscle actin, matrix metalloproteinase MMP-2 and MMP-8) decreased in the MSC-treated group. Moreover, PCR showed lower expression of genes encoding molecules associated with inflammation (TNF- α , IL-1 β) and higher expression of genes encoding anti-inflammatory molecules (IL-10) in the group treated with stem cells [33].

Discussion

The aim of this review was to collect clinical studies and present the latest discoveries on the use of stem cells in the treatment of diabetes and its complications. Animal studies [9,10] have shown that injections using stem cells can reduce blood glucose levels by secreting insulin. Moreover, in studies involving patients with type 1 diabetes [11,12,13], which assessed more parameters, a number of positive effects of stem cells were found. A decrease in the concentration of glycated hemoglobin, a decrease in the concentration of proinflammatory cytokines and an increase in anti-inflammatory cytokines, as well as a decrease in the concentration of antibodies characteristic in this disease were observed. In one of the studies focusing on patients with type 2 diabetes [14], it was noted that stem cell therapy could have an impact on reducing the doses of hypoglycemic drugs, and in one patient from the research group it was possible to completely discontinue the drugs, which is of great importance because it reduces the occurrence of side effects associated with the use of these drugs. Moreover, during the studies [13,14,15,16], no serious negative effects of stem cells were observed, which allows us to assume that this therapy can be safe for patients. It is worth mentioning the limitations of these studies, which undoubtedly include small groups of patients. The duration of the disease and the patient's initial body weight are factors that may also affect the effects of stem cell therapy, which is why the test results may lead to different conclusions [15]. To systematize this, further studies should be conducted involving larger groups of patients with similar disease duration and similar body weight to eliminate these

variables as the cause of unreliable results. Stem cells can significantly improve the function of kidneys damaged in diabetes by inhibiting interstitial fibrosis, reducing inflammatory infiltration, and also improve renal parameters (creatinine and urea concentration) [18,19]. In the case of diabetic neuropathy [21], the use of stem cells was associated with improved nerve conduction and axon myelination. Preventing visual dysfunction in the course of diabetic retinopathy is another positive effect of stem cells. In the study [29], this was associated with a positive effect on the survival time of retinal cells, especially ganglion cells and bipolar rod cells. However, these results only apply to the animal model. Another study involving patients with chronic ulcers [26] noted a significantly faster healing time of these wounds (on average half as long) in the group using stem cells. An interesting aspect worth mentioning is financial issues, because in the case of, for example, ulcer treatment [27], the cost of therapy was significantly higher in group using stem cells. However, the treatment time was shorter, which may be more profitable for the patient in the long run. Many issues regarding this treatment method are still uncertain, further research is needed, especially on large, diverse groups of patients, to be able to determine for whom the therapy will be appropriate and predict what effect it will have. However, the research conducted so far shows that the method has potential and may be an alternative to pharmacological treatment in the future.

Conclusions

Diabetes is a common condition and the total number of people suffering from it is constantly increasing. Despite the treatment, the risk of complications increases with the duration of the disease. Therefore, it is important to research new methods that could facilitate treatment and delay or completely stop the progression of organ damage. Stem cells are a promising object of analysis in this respect (they can control glycemia, and also have a positive effect on the functioning of the kidneys, heart, eyes, nerves, accelerate wound healing), but further, extensive research is needed to assess the effectiveness and safety of this therapy.

Author's contribution

Conceptualization: Łukasz Ochyra, Anna Łopuszyńska; methodology: Łukasz Ochyra, Anna Łopuszyńska; software: Łukasz Ochyra, Anna Łopuszyńska, check: Łukasz Ochyra, Anna Łopuszyńska; formal analysis: Łukasz Ochyra, Anna Łopuszyńska; investigation: Łukasz Ochyra, Anna Łopuszyńska; resources: Łukasz Ochyra, Anna Łopuszyńska; data curation: Łukasz Ochyra, Anna Łopuszyńska; writing- rough preparation: Łukasz Ochyra, Anna Łopuszyńska; writing- review and editing: Łukasz Ochyra, Anna Łopuszyńska; visualization: Łukasz Ochyra, Anna Łopuszyńska; supervision: Łukasz Ochyra, Anna Łopuszyńska; project

administration: Łukasz Ochyra, Anna Łopuszyńska; receiving funding: Łukasz Ochyra, Anna Łopuszyńska.

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