

Type 2 diabetes mellitus

According to a recent World Health Organisation report diabetes mellitus is one of the top ten leading causes of death worldwide[1]. Also advanced diabetes mellitus is associated with significant cardiovascular, nervous and renal complications. Among patients with diagnosed diabetes mellitus, 95% have type 2 diabetes which mainly develops at an adult age (more than 25 years)[2]. Type 2 diabetes mellitus is characterized by a combination of insulin resistance and pancreatic beta-cell dysfunction, which begin to secrete reduced insulin amounts in response to increased glycemic values[3]. Initially type 2 diabetes mellitus can be treated by oral hypoglycemic medication. The existed data demonstrate that 27% patients with type 2 diabetes mellitus eventually become insulin dependent. Moreover, since exogenous insulin cannot provide the tight glycemic control in comparison with the pancreas-derived insulin, less than one half patients with type 2 diabetes mellitus achieve the recommended Hb A1c level[4].

Stem cell therapy for Type 2 diabetes mellitus

Stem cell therapy represents a promising alternative for type 2 diabetic patients who fail to control hyperglycemia even with insulin injection. Today several clinical trials have been conducted in which the positive action of stem cells in patients with type 2 diabetes mellitus was showed.

In recent clinical research it was demonstrated that using of autologous bone marrow stem cells with hyperbaric oxygen treatment before and after injection of stem cells can improve islet function and metabolic control in patients with type 2 diabetes mellitus. This study enrolled 25 patients with type 2 diabetes mellitus (seventeen male and eight female) who received a combination therapy (autologous bone marrow stem cells with hyperbaric oxygen treatment before and after injection). All metabolic variables (fasting glucose, HbA1c, fasting C-peptide, C-peptide/glucose ratio and insulin requirements) showed significant improvement when comparing baseline to 12 months follow-up[5].

In 2009 Bhansali et al. reported the results of the prospective study in which they used autologous bone marrow stem cells for the treatment of patients with type 2 diabetes mellitus. A total of 10 patients with type 2 diabetes mellitus who fail to control hyperglycemia by triple oral antidiabetic drugs and currently on insulin were included. Seven patients showed reduced insulin requirements by 75% from baseline. Moreover, three subjects achieved insulin independence. Also reduced HbA1c values were recorded in these patients. In addition to improved metabolic control there were amelioration of fasting and glucagonstimulated C-peptide levels and increased HOMA-B (score for assessment of beta-cell function). It is important to emphasize that no serious adverse effects were recorded in this trial[6].

Treatment the patients with type 2 diabetes mellitus by using mesenchymal stem cells was implemented in clinical research by Jiang R et al. in 2011. There were ten patients with long duration type 2 diabetes mellitus who used high insulin doses and failed to achieve satisfying levels of glucose. All patients received three intravenous infusions of mesenchymal stem cells with one month interval between infusions. At the end of follow-up period (3 months) a daily mean dose of insulin was decreased in all patients significantly. Also, the C-peptide level was increased.

Moreover, it was demonstrated that the renal function and cardiac function were improved after infusion. It should be noted that no side effects were reported[7].

Encouraging results were obtained in clinical research conducted by Liu X et al. in the beginning of the year 2014. It was a prospective study in which mesenchymal stem cells were used in the treatment of patients with type 2 diabetes mellitus. Twenty-two patients were enrolled in the study. All of them received mesenchymal stem cells. The clinical study demonstrated improvement in beta cell function and C-peptide levels. Also, significant decrease of glucose level and glycosylated hemoglobin was observed in all patients. It is necessary to mention that reduced markers of systemic inflammation and T lymphocyte counts were also detected in all patients. Importantly to note, that no transplantation-related adverse events were reported[8].

One of the most common complications in patients with diabetes mellitus is foot ulceration which is a consequence of hyperglycemia-induced damages of the peripheral nerve and vasculature[9]. Because of physiological impairments in wound healing and an increased susceptibility to infection closure of the foot wound is hampered in patients with diabetes mellitus. Also, non-healing foot ulcers can lead to amputation of lower limb[10]. More than 60% of nontraumatic amputations are performed in patients with diabetes mellitus. This is a significant burden for the society[11].

In recent years, mesenchymal stem cells has been considered as a new therapeutic option for diabetic foot ulcers due to possibility of their migration to the sites of injury and improvement wound healing by stimulating angiogenesis and promoting revascularization[12].

In 2009 Dash NR et al. demonstrated the efficacy and feasibility of using autologous bone marrow derived mesenchymal stem cells in the treatment of chronic nonhealing diabetic foot ulcers. This clinical research included 24 patients with nonhealing ulcers of the lower limb who were randomized into implant and control groups. After a 12-week period of follow-up the implant group had significant improvement in pain-free walking distance and reduction in ulcer size as compared to control group. Also, conducted biopsy of implanted tissues showed development of dermal cells(mainly fibroblasts), including mature and immature inflammatory cells which allowed to conclude that autologous implantation of bone marrow derived mesenchymal stem cells in nonhealing ulcers accelerates the healing process[13].

It is necessary to mention encouraging results which have been obtained in experimental trial with animal models. These studies have explored the potential role of mesenchymal stem cells in the management of diabetic complications such as diabetic nephropathy and diabetic neuropathy. It was demonstrated that using of mesenchymal stem cells led to attenuation of microalbuminuria and amelioration of renal function[14]. Also, Kim et al. showed improvement in the vascularity of the nerve and normalization of nerve conduction velocity after intramuscularly injection of bone marrow derived mesenchymal stem cells[15].

In conclusion, cell-based therapy for diabetes mellitus represents a highly promising therapeutic approach. According to existing observations using of mesenchymal stem cells in the treatment of patients with diverse pathologies is safe. Furthermore, to date mesenchymal stem cells have been administered to more than 1,000 human patients with no evidence of adverse effects or tumor formation[16].

References

1. **WHO Report** Burden: mortality, morbidity and risk factors-WHO report, Global Status Report on NCDs, 2010.
2. **El-Badri N et al.** Mesenchymal stem cell therapy in diabetes mellitus: progress and challenges. *J Nucleic Acids*. 2013;2013:194858. doi: 10.1155/2013/194858. Epub 2013 May 15.
3. **Fotino C et al.** Bone marrow-derived stem cell transplantation for the treatment of insulin-dependent diabetes. *Rev Diabet Stud*. 2010 Summer;7(2):144-57. doi: 10.1900/RDS.2010.7.144. Epub 2010 Aug 10.
4. **Koro C.E. et al.** Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report, *Diabetes Care*, vol. 27, no. 1, pp. 17–20, 2004.
5. **Estrada E.J. et al.** Combined treatment of intrapancreatic autologous bone marrow stem cells and hyperbaric oxygen in type 2 diabetes mellitus. *Cell Transplant* 2008. 17:1295-1304.
6. **Bhansali A et al.** Efficacy of autologous bone marrow derived stem cell transplantation in patients with type 2 diabetes mellitus. *Stem Cells Dev* 2009. 18(10):1407-1416.
7. **Jiang R et al.** Transplantation of placenta-derived mesenchymal stem cells in type 2 diabetes: a pilot study. *Front Med*. 2011 Mar;5(1):94-100. doi: 10.1007/s11684-011-0116-z. Epub 2011 Mar 17.
8. **Liu X et al.** A preliminary evaluation of efficacy and safety of Wharton's jelly mesenchymal stem cell transplantation in patients with type 2 diabetes mellitus. *Stem Cell Res Ther*. 2014 Apr 23;5(2):57. doi: 10.1186/scrt446.
9. **Weck M et al.** Noninvasive management of the diabetic foot with critical limb ischemia: current options and future perspectives. *Therapeut Adv Endocrinol Metabol* 2011; 2: 247-55.
10. **Bowering CK.** Diabetic foot ulcers: pathophysiology, assessment, and therapy. *Can Fam Physician* 2001; 47:1007–1016
11. **Dalla Paola L et al.** Treatment of diabetic foot ulcer: an overview strategies for clinical approach. *Curr Diabetes Rev* 2006; 2: 431-47.
12. **Dash SN et al.** Towards reaching the target: clinical application of mesenchymal stem cells for diabetic foot ulcers. *Rejuvenation Res*. 2014 Feb;17(1):40-53. doi: 10.1089/rej.2013.1467.
13. **Dash NR et al.** Targeting nonhealing ulcers of lower extremity in human through autologous bone marrow-derived mesenchymal stem cells. *Rej Res* 2009; 12: 359– 366.
14. **Ezquer F. E. et al.** Systemic administration of multipotent mesenchymal stromal cells reverts hyperglycemia and prevents nephropathy in type 1 diabetic mice. *Biol Blood Marrow Transplant* 2008; 14:631-640
15. **Kim, H et al.** Bone marrow mononuclear cells have neurovascular tropism and improve diabetic neuropathy. *Stem Cells* 2009; 27(7), 1686-1696.
16. **Ezquer M. E. et al.** MSCs transplantation: a promising therapeutic strategy to manage the onset and progression of diabetic nephropathy,” *Biological Research*, vol. 45, pp. 289–296, 2012.



3 INTERNATIONAL CLINICS

50 HIGHLY SKILLED MEDICAL EXPERTS

ADVANCED MEDICAL EQUIPMENT

PATIENTS FROM ALL OVER THE WORLD



