12.
BÖLÜM

Tip 1 Diyabette Mezenkimal Kök Hücrelerin Etkinliğinin Değerlendirilmesi

Gökçen GÖKÇE[1]

GİRİŞ

Diyabet (DM) insülinin salınımında, etkisinde veya bu her iki faktörün mekanizmasında meydana gelen bozukluğa bağlı olarak karbonhidrat, protein ve yağ metabolizmasındaki değişiklikler ile karakterize edilen, glisemik kontrolün sağlanması ve risk azaltma stratejileri sebebiyle devamlı tıbbi bakım ve yardım gerektiren, çok yönlü, endokrinolojik ve kronik bir metabolizma hastalığıdır. Klinik bulgu ve belirtileri arasında kilo kayıpları, ciltte meydana gelen kurumalar, görme bozuklukları, el ve ayaklarda görülen uyuşma ve karıncalanmalar, idrar yolu enfeksiyonları, polidipsi, polifaji, poliüri, mantar enfeksiyonları, halsizlik ve yorgunluk bulunmaktadır. Çok yönlü ve kronik bir hastalık olması nedeniyle diayebetin tedavi ile etkinliğinin sağlanamadığı durumlarda hiperglisemiye bağlı akut komplikasyonlar meydana gelmekte ve ölümlere yol açabilmektedir (1-6). Hastalığın iyileştirilmesi için harcanan emek ve zaman, sakatlıklar, erken ölümler, uzun dönemde meydana gelen komplikasyonlar ve sebep olduğu ek maliyetler yönünden ele alındığında hastalık ülke ekonomisine ve sağlik sistemine büyük mali yük oluşturmaktadır. ABD'de 2015 yılı itibariyle 30 milyondan fazla kişi de diyabet hastası olarak açıklanmıştır ve bu durum tip 2 diyabet ve diğer kronik hastalıkları riskini artıran ciddi bir sağlık sorunudur (1, 7-9).

DM tedavisinde insülin analogları, pankreas adacık nakilleri ve son yıllarda artan sayıda çalışmalarla desteklenen alternatif kök hücre uygulamaları yapılmaktadır (3, 10-13). Kök hücre tedavisi, kendini yenileme ve onarma özelliği olmayan hücrelerin kaybıyla gelişen diyabet gibi hastalıklarda kök hücrelerin

[1] Arş. Gör., Ankara Üniversitesi Tıp Fakültesi, gkcgkcn@hotmail.com

KAYNAKÇA

1. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes. Endocrinology and metabolism clinics of North America. 2010;39(3):481-97.
2. Bluestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. Nature. 2010;464(7293):1293-300.
3. Katsarou A, Gudbjörnsdottir S, Rawshani A, Dabelea D, Bonifacio E, Anderson BJ, et al. Type 1 diabetes mellitus. Nature reviews Disease primers. 2017;3:17016.
4. Lechleitner M, Hoppichler F, Kaser S. [Autoimmune diseases in type 1 diabetes]. Wiener klinische Wochenschrift. 2016;128 Suppl 2:S201-3.
5. Schmidt AM. Highlighting Diabetes Mellitus: The Epidemic Continues. Arteriosclerosis, thrombosis, and vascular biology. 2018;38(1):e1-e8.
6. Acharjee S, Ghosh B, Al-Dhubiab BE, Nair AB. Understanding type 1 diabetes: etiology and models. Canadian journal of diabetes. 2013;37(4):269-76.
7. Xia Y, Xie Z, Huang G, Zhou Z. Incidence and trend of type 1 diabetes and the underlying environmental determinants. Diabetes Metab Res Rev. 2019;35(1):e3075.
8. Rogers MAM, Kim C, Banerjee T, Lee JM. Fluctuations in the incidence of type 1 diabetes in the United States from 2001 to 2015: a longitudinal study. BMC Med. 2017;15(1):199.
9. Xu G, Liu B, Sun Y, Du Y, Snetselaar LG, Hu FB, et al. Prevalence of diagnosed type 1 and type 2 diabetes among US adults in 2016 and 2017: population based study. BMJ (Clinical research ed). 2018;362:k1497.
10. Aguayo-Mazzucato C, Bonner-Weir S. Stem cell therapy for type 1 diabetes mellitus. Nature reviews Endocrinology. 2010;6(3):139-48.
11. Domínguez-Bendala J, Lanzoni G, Inverardi L, Ricordi C. Concise review: mesenchymal stem cells for diabetes. Stem cells translational medicine. 2012;1(1):59-63.
12. Haak T, Gölz S, Fritsche A, Füchtenbusch M, Siegmund T, Schnellbächer E, et al. Therapy of Type 1 Diabetes. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association. 2019;127(S 01):S27-s38.
13. Li L, Li F, Gao F, Yang Y, Liu Y, Guo P, et al. Transplantation of mesenchymal stem cells improves type 1 diabetes mellitus. Cell and tissue research. 2016;364(2):345-55.
14. Anzalone R, Iacono ML, Loria T, Di Stefano A, Giannuzzi P, Farina F, et al. Wharton's jelly mesenchymal stem cells as candidates for beta cells regeneration: extending the differentiative and immunomodulatory benefits of adult mesenchymal stem cells for the treatment of type 1 diabetes. Stem Cell Reviews and Reports. 2011;7(2):342-63.
15. Ezquer F, Ezquer M, Contador D, Ricca M, Simon V, Conget P. The antidiabetic effect of mesenchymal stem cells is unrelated to their transdifferentiation potential but to their capability to restore Th1/Th2 balance and to modify the pancreatic microenvironment. Stem cells (Dayton, Ohio). 2012;30(8):1664-74.
16. Davies LC, Alm JJ, Heldring N, Moll G, Gavin C, Batsis I, et al. Type 1 diabetes mellitus donor mesenchymal stromal cells exhibit comparable potency to healthy controls in vitro. Stem cells translational medicine. 2016;5(11):1485-95.
17. Evans MJ, Kaufman MH. Establishment in culture of pluripotential cells from mouse embryos. Nature. 1981;292(5819):154-6.

18. Thomson JA, Kalishman J, Golos TG, Durning M, Harris CP, Becker RA, et al. Isolation of a primate embryonic stem cell line. Proceedings of the National Academy of Sciences of the United States of America. 1995;92(17):7844-8.
19. Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, et al. Embryonic stem cell lines derived from human blastocysts. Science (New York, NY). 1998;282(5391):1145-7.
20. Paschou SA, Papadopoulou-Marketou N, Chrousos GP, Kanaka-Gantenbein C. On type 1 diabetes mellitus pathogenesis. Endocrine connections. 2018;7(1):R38-R46.
21. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. Lancet (London, England). 2018;391(10138):2449-62.
22. De Ferranti SD, De Boer IH, Fonseca V, Fox CS, Golden SH, Lavie CJ, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Circulation. 2014;130(13):1110-30.
23. Mâncio RD, Minatel E, de Almeida Cardoso M, Ali Khan B, José Caldeira E. The immunomodulation to diabetes control: New proposals for the reversion of this disease. Diabetes & metabolic syndrome. 2015;9(4):210-2.
24. Hodgson B, Mafi R, Mafi P, Khan W. The regulation of differentiation of mesenchymal stem-cells into skeletal muscle: a look at signalling molecules involved in myogenesis. Current stem cell research & therapy. 2018;13(5):384-407.
25. Borakati A, Mafi R, Mafi P, Khan WS. A systematic review and meta-analysis of clinical trials of mesenchymal stem cell therapy for cartilage repair. Current stem cell research & therapy. 2018;13(3):215-25.
26. Davis NE, Hamilton D, Fontaine MJ. Harnessing the immunomodulatory and tissue repair properties of mesenchymal stem cells to restore β cell function. Current diabetes reports. 2012;12(5):612-22.
27. Baer PC, Geiger H. Adipose-derived mesenchymal stromal/stem cells: tissue localization, characterization, and heterogeneity. Stem cells international. 2012;2012:812693.
28. Matur İ, Solmaz S. Kök Hücre Üretiminde Güncel Yaklaşımlar. Arşiv Kaynak Tarama Dergisi. 2011;20(3):168-86.
29. Ra JC, Kang SK, Shin IS, Park HG, Joo SA, Kim JG, et al. Stem cell treatment for patients with autoimmune disease by systemic infusion of culture-expanded autologous adipose tissue derived mesenchymal stem cells. Journal of translational medicine. 2011;9:181.
30. Kim M, Kim C, Choi YS, Kim M, Park C, Suh Y. Age-related alterations in mesenchymal stem cells related to shift in differentiation from osteogenic to adipogenic potential: implication to age-associated bone diseases and defects. Mechanisms of ageing and development. 2012;133(5):215-25.
31. Wang S, Qu X, Zhao RC. Clinical applications of mesenchymal stem cells. Journal of hematology & oncology. 2012;5:19.
32. Bassi EJ, Aita CA, Câmara NO. Immune regulatory properties of multipotent mesenchymal stromal cells: Where do we stand? World journal of stem cells. 2011;3(1):1-8.
33. Kern S, Eichler H, Stoeve J, Klüter H, Bieback K. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. Stem cells (Dayton, Ohio). 2006;24(5):1294-301.

34. Hu L, Hu J, Zhao J, Liu J, Ouyang W, Yang C, et al. Side-by-side comparison of the biological characteristics of human umbilical cord and adipose tissue-derived mesenchymal stem cells. BioMed research international. 2013;2013.
35. Lee YS, Lee J-E, Park H-Y, Lim Y-S, Lee J-C, Wang S-G, et al. Isolation of mesenchymal stromal cells (MSCs) from human adenoid tissue. Cellular Physiology and Biochemistry. 2013;31(4-5):513-24.
36. Ra JC, Shin IS, Kim SH, Kang SK, Kang BC, Lee HY, et al. Safety of intravenous infusion of human adipose tissue-derived mesenchymal stem cells in animals and humans. Stem cells and development. 2011;20(8):1297-308.
37. Ghannam S, Bouffi C, Djouad F, Jorgensen C, Noël D. Immunosuppression by mesenchymal stem cells: mechanisms and clinical applications. Stem Cell Res Ther. 2010;1(1):2.
38. Liu Y, Wang S, Shi S. The role of recipient T cells in mesenchymal stem cell-based tissue regeneration. The international journal of biochemistry & cell biology. 2012;44(11):2044-50.
39. Brooke G, Cook M, Blair C, Han R, Heazlewood C, Jones B, et al. Therapeutic applications of mesenchymal stromal cells. Seminars in cell & developmental biology. 2007;18(6):846-58.
40. Bellin MD, Barton FB, Heitman A, Harmon JV, Kandaswamy R, Balamurugan AN, et al. Potent induction immunotherapy promotes long-term insulin independence after islet transplantation in type 1 diabetes. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2012;12(6):1576-83.
41. Banerjee S. Prevention of diabetes. Journal of the Indian Medical Association. 2003;101(12):698-9.
42. Wu H, Mahato RI. Mesenchymal stem cell-based therapy for type 1 diabetes. Discovery medicine. 2014;17(93):139-43.
43. Zhang ZY, Zhou ZQ, Song KB, Kim SC, Zhou GW. Hepatic stellate cells induce immunotolerance of islet allografts. Transplantation proceedings. 2014;46(5):1594-600.
44. Grapensparr L, Vasylovska S, Li Z, Olerud J, Jansson L, Kozlova E, et al. Co-transplantation of human pancreatic islets with post-migratory neural crest stem cells increases β-cell proliferation and vascular and neural regrowth. The Journal of clinical endocrinology and metabolism. 2015;100(4):E583-90.
45. Coronel MM, Stabler CL. Engineering a local microenvironment for pancreatic islet replacement. Current opinion in biotechnology. 2013;24(5):900-8.
46. Pagliuca FW, Millman JR, Gürtler M, Segel M, Van Dervort A, Ryu JH, et al. Generation of functional human pancreatic β cells in vitro. Cell. 2014;159(2):428-39.
47. Rezania A, Xu J. Differentiation of pluripotent stem cells to definitive endoderm lineage. Google Patents; 2014.
48. Rezania A, Bruin JE, Arora P, Rubin A, Batushansky I, Asadi A, et al. Reversal of diabetes with insulin-producing cells derived in vitro from human pluripotent stem cells. Nature biotechnology. 2014;32(11):1121.
49. Mahgoub MA, Ammar A, Fayez M, Edris A, Hazem A, Akl M, et al. Neovascularization of the amniotic membrane as a biological immune barrier. Transplantation proceedings. 2004;36(4):1194-8.

50. Figliuzzi M, Cornolti R, Perico N, Rota C, Morigi M, Remuzzi G, et al. Bone marrow-derived mesenchymal stem cells improve islet graft function in diabetic rats. Transplantation proceedings. 2009;41(5):1797-800.
51. Mundra V, Gerling IC, Mahato RI. Mesenchymal stem cell-based therapy. Molecular pharmaceutics. 2013;10(1):77-89.
52. Paek HJ, Kim C, Williams SK. Adipose stem cell-based regenerative medicine for reversal of diabetic hyperglycemia. World journal of diabetes. 2014;5(3):235-43.
53. Khan WS, Hardingham TE. The characterisation of mesenchymal stem cells: a stem cell is not a stem cell is not a stem cell. Journal of Stem Cells. 2012;7(2):87.
54. Li L, Li F, Gao F, Yang Y, Liu Y, Guo P, et al. Transplantation of mesenchymal stem cells improves type 1 diabetes mellitus. Cell and tissue research. 2016;364(2):345-55.
55. Itkin-Ansari P, Demeterco C, Bossie S, de la Tour DD, Beattie GM, Movassat J, et al. PDX-1 and cell-cell contact act in synergy to promote delta-cell development in a human pancreatic endocrine precursor cell line. Molecular endocrinology (Baltimore, Md). 2000;14(6):814-22.
56. BİLGİN LGY, DÜZGÜN ŞATD. Kök hücre çalışmalarının ortaya çıkardığı sorunlara etik ve teolojik bir yaklaşım 2011.
57. Miao G, Ostrowski RP, Mace J, Hough J, Hopper A, Peverini R, et al. Dynamic production of hypoxia-inducible factor-1alpha in early transplanted islets. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2006;6(11):2636-43.
58. Madec AM, Mallone R, Afonso G, Abou Mrad E, Mesnier A, Eljaafari A, et al. Mesenchymal stem cells protect NOD mice from diabetes by inducing regulatory T cells. Diabetologia. 2009;52(7):1391-9.
59. Ankrum J, Karp JM. Mesenchymal stem cell therapy: Two steps forward, one step back. Trends Mol Med. 2010;16(5):203-9.
60. Gorabi AM. A., Farhad, Souri, Mona, Jahandideh, Kazempor (2016). Mesenchymal Stem Cells (MSC) Effect in Streptozotocin (STZ) Induced Type I Diabetic Rats. The Caspian Sea Journal.1:91-5.