

Bölüm 42

PANKREAS VE ADACIK HÜCRE NAKLİ

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GİRİŞ

Dünyada, diyabetin görülme sıklığı son 30 yılda yaklaşık 2 kat artmıştır ve bu artış özellikle orta ve düşük gelirli ülkelerde daha hızlı olmuştur (1). Dünya sağlık örgütünün raporuna göre, 2016 yılında diyabet ile ilişkili ölüm 1.6 milyon olarak bildirilmiştir (1). Ölümün dışında diyabete bağlı mikro ve makro vasküler komplikasyon sonucu gelişen, diyabetik nefropati, nöropati ve retinopati nedeniyle oluşan sağlık sorunları, tüm dünyada önemli mali ve sosyal yük oluşturmuştur (2).

Bugün pankreas nakli, esas olarak tip 1 diyabet (T1DM) tedavisinde ağırlıklı olarak kullanılır (3, 4). Bozulmuş glikoz homeostazını, hipoglisemi ya da hiperglisemi atakları olmadan sağlayabilecek tek tedavi seçeneğidir (5). Bazı tip 2 diyabet olgularında, insülin direnci ile birlikte aynı zamanda düşük miktarda insülin yapımı vardır ve bu hastalarda pankreas nakli gerekebilir. Tüm dünyada yapılan pankreas nakillerinin %10'unu bu şekilde tip 2 diyabet hastalarına uygulanmıştır. Pankreas nakillerinin çok az bir bölümü ise pankreasın benign tümörleri ve kronik pankreatit nedeniyle gerçekleştirilmiştir (Tablo-1).

Pankreas nakli pankreasın ekzokrin ve endokrin fonksiyonlarını içerecek şekilde organın bütün olarak nakledilmesi veya yalnızca endokrin fonksiyonlarını içeren adacık hücre nakli şeklinde yapılmaktadır.

Pankreas Nakli

İlk insan pankreas nakli, 1966'da Minnesota üniversitesinde, Kelly ve ark. tarafından uygulanmıştır (6). 1980'lerde, pankreas gövde ya da kuyruk kısımlarını içeren segmental pankreas nakilleri gerçekleştirilmiştir (3). İmmunosupresyon ve cerrahi tekniklerdeki gelişmeler sonucunda yapılan nakil sayısı artmıştır.

Medikal tedaviye yanıt vermeyen hastalar başta olmak üzere pankreas nakli yapılacak hastanın seçiminin dikkatli yapılması gerekmektedir. Son zamanlarda pankreas ile sınırlı malign tümörler ve travmatik pankreas yaralanmalarında da nakil uygulanmıştır (7,8).

Pankreas nakli başlıca 3 ana tipte yapılır;

- Böbrek fonksiyonları normal ya da minimal bozukluk taşıyan diyabetli hastalarda, yalnızca pankreas nakledilir (soliter pankreas nakli (PTA)).
- Böbrek yetmezliği bulunan diyabetli hastada eş zamanlı, kombine böbrek ve pankreas (SPK) nakli şeklinde yapılabilen tip.
- Eş zamanlı olarak hem böbrek hem de pankreas bulunmadığı zamanlarda, ilk önce kadaverik ya da canlı vericiden böbrek nakli ve ardından uygun zamanda pankreasın (PAK) naklidir.

SPK %80 oranında uygulanırken, PAK %15 ve PTA ise sadece %5 oranında uygulanmıştır (9).

Pankreatik greft temini, genellikle multiple organ nakli esnasında, karaciğer ile birlikte blok

ne kadar 6 olguda Dünyada ise 2014 yılına kadar 48.301 hastada pankreas nakli gerçekleştirilmiştir. Tüm dünyada diyabet ya da diğer nedenlerle insüline bağımlılık düşünüldüğünde nakil yapılması gereken hasta sayısı ile yapılan nakil oranının ne kadar düşük olduğu görülecektir. Bu nedenle pankreas temininde yaşanan kısıtlılığın ortadan kaldırılması için, mezenkimal stem cell gibi yeni kaynak ve yeni tekniklerin geliştirilmesi için yoğun çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Allojenik Adacık hücre transplantasyonu, Pankreas transplantasyonu, Pankreas otolog adacık hücre transplantasyonu

KAYNAKLAR

1. http://apps.who.int/healthinfo/statistics/mortality/causeofdeath_query/, accessed 12 July 2019.
2. Collins AJ, Foley R, Herzog C, et al. Excerpts from the United States Renal Data System 2007 annual data report. *Am J Kidney Dis* 2008; 51:S1–S320.
3. Sutherland DE, Gruessner RW, Dunn DL, et al. Lessons learned from more than 1,000 pancreas transplants at a single institution. *Ann Surg* 2001; 233:463–501.
4. Mittal S, Gough SC. Pancreas transplantation: a treatment option for people with diabetes. *Diabet Med* 2014; 31:512–21.
5. Cottrell DA, Henry ML, O'Dorisio TM, et al. Hypoglycemia after successful pancreas transplantation in type I diabetic patients. *Diabetes Care*. 1991; 14:1111–1113.
6. Kelly WB, Lillehei RC, Merkel FK, et al. Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. *Transplantation* 1968; 6:145.
7. Balzano G, Carvello M, Piemonti L, et al. Combined laparoscopic spleen-preserving distal pancreatectomy and islet autotransplantation for benign pancreatic neoplasm. *World J Gastroenterol*. 2014 Apr 14;20(14):4030–6. doi: 10.3748/wjg.v20.i14.4030.
8. Jindal RM, Ricordi C, Shriver CD. Autologous pancreatic islet transplantation for severe trauma. *N Engl J Med*. 2010;362(16):1550. doi:10.1056/NEJMc0912392
9. Clatworthy M, Watson C, Allison M, Dark J. 2012. *Transplantation at a Glance*. 1st edn. John Wiley & Sons.
10. Imagawa DK, Olthoff KM, Yersiz H, et al. Rapid end bloc technique for pancreas-liver procurement. Improved early liver function. *Transplantation* 1996; 61:1605–9.
11. Rogers J, Farney AC, Orlando G, et al. Pancreas transplantation with portal venous drainage with an emphasis on technical aspects. *Clin Transplant* 2014; 28:16–26.
12. Hakim NS, Gruessner AC, Papalois BE, et al. Duodenal complications in bladder-drained pancreas transplantation. *Surgery* 1997; 121:618–24.
13. Bloom RD, Olivares M, Rehman L, et al. Long-term pancreas allograft outcome in simultaneous pancreas and kidney transplantation: a comparison of enteric and bladder drainage. *Transplantation* 1997; 64:1689–95.
14. Rosenlof LK, Earnhardt RC, Pruett TL, et al. Pancreas transplantation. An initial experience with systemic and portal drainage of pancreatic allografts. *Ann Surg* 1992;215:586.
15. Gruessner RW, Gruessner AC. The current state of pancreas transplantation. *Nat Rev Endocrinol* 2013; 9: 555–562. DOI: 10.1038/nrendo.2013.138.
16. Ruiz P. *Transplantation pathology*. Cambridge University Press 2018: United Kingdom, 2. Edition: Chapter 1: p.1–24.
17. Mc Call M, Shapiro AM. Islet cell transplantation. *Semin Pediatr Surg* 2014;23(2):83–90.
18. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure and its component syndromes in diabetes. *Diabetes* 2005;54(12):3592–3601
19. Thompson DM, Begg IS, Harris C, et al. Reduced progression of diabetic retinopathy after islet cell transplantation compared with intensive medical therapy. *Transplantation* 2008;85(10):1400–1405.
20. Thompson DM, Meloche M, Ao Z, et al. Reduced progression of diabetic microvascular complications with islet cell transplantation compared with intensive medical therapy. *Transplantation* 2011;91(3):373–378.
21. Lacy PE, Kostianovsky M. Method for the isolation of intact islets of Langerhans from the rat pancreas. *Diabetes* 1967;16(1):35–39.
22. Najarian JS, Sutherland DE, Matas AJ, et al. Human islet transplantation: a preliminary report. *Transplant Proc* 1977;9 (1):233–236
23. Ricordi C, Lacy PE, Finke EH, et al. Automated method for isolation of human pancreatic islets. *Diabetes* 1988;37(4):413–420.
24. Carroll PB, Ricordi C, Rilo HR, et al. Intrahepatic human islet transplantation at the University of Pittsburgh: results in 25 consecutive cases. *Transplant Proc* 1992;24(6):3038–3039.
25. Shapiro AM, Ricordi C, Hering BJ, et al. International trial of the Edmonton protocol for islet transplantation. *N Engl J Med* 2006;355(13):1318–1330
26. Bruni A, Gala-Lopez B, Pepper AR, et al. Islet cell transplantation for the treatment of type 1 diabetes: recent advances and future challenges. *Diabetes Metab Syndr Obes* 2014;7:211–223.
27. CIT website: <http://www.citisletstudy.org/>, accessed 12 July 2019.
28. Balamurugan AN, Loganathan G, Lockridge A, et al. 2014. Islet isolation from pancreatitis pancreas for autologous islet isolation. In: Islam MS (ed) *Islet of langerhans*, 2nd edn. vol. 1. pp. 1199–1227, Springer Reference, USA.
29. Noguchi H. Pancreas procurement and preservation for islet transplantation: personal considerations. *J Transplant* 2011;783168
30. Fujino Y. Two-layer cold storage method for pancreas and islet cell transplantation. *World J Gastroenterol* 2010;16(26):3235–3238
31. Lakey JR, Burridge PW, Shapiro AM. Technical aspects of islet preparation and transplantation. *Transpl Int* 2003;16(9):613–632.

32. Loganathan G, Dawra RK, Pugazhenth S, et al. Insulin degradation by acinar cell proteases creates a dysfunctional environment for human islets before/after transplantation: benefits of alpha-1 antitrypsin treatment. *Transplantation* 2011;92 (11):1222–1230
33. Froud T, Ricordi C, Baidal DA, et al. Islet transplantation in type 1 diabetes mellitus using cultured islets and steroid-free immunosuppression: Miami experience. *Am J Transplant* 2005;5(8):2037–2046.
34. Hering BJ, Kandaswamy R, Ansite JD, et al. Single-donor, marginal-dose islet transplantation in patients with type 1 diabetes. *JAMA* 2005;293(7):830–835.
35. Papas KK, Suszynski TM, Colton CK. Islet assessment for transplantation. *Curr Opin Organ Transplant* 2009;14(6):674–682.
36. Markmann JF, Deng S, Huang X, et al. Insulin independence following isolated islet transplantation and single islet infusions. *Ann Surg* 2003;237(6):741–749; discussion 749–750.
37. Barton FB, Rickels MR, Alejandro R, et al. Improvement in outcomes of clinical islet transplantation: 1999–2010. *Diabetes Care* 2012;35(7):1436–1445.
38. Bellin MD, Barton FB, Heitman A, et al. Potent induction immunotherapy promotes long-term insulin independence after islet transplantation in type 1 diabetes. *Am J Transplant* 2012;12(6):1576–1583
39. Balamurugan AN, Naziruddin B, Lockridge A, et al. Islet product characteristics and factors related to successful human islet transplantation from the Collaborative Islet Transplant Registry (CITR) 1999–2010. *Am J Transplant* 2014;14(11):2595–2606.
40. Cabric S, Sanchez J, Lundgren T, et al. Islet surface heparinization prevents the instant blood-mediated inflammatory reaction in islet transplantation. *Diabetes* 2007;56(8):2008–2015.
41. Naziruddin B, Iwahashi S, Kanak MA, et al. Evidence for instant blood-mediated inflammatory reaction in clinical autologous islet transplantation. *Am J Transplant* 2014;14(2):428–437.
42. Sutherland DE, Radosevich DM, Bellin MD, et al. Total pancreatectomy and islet autotransplantation for chronic pancreatitis. *J Am Coll Surg* 2012; 214(4):409–424; discussion 424–406. doi: 10.1016/j.jamcollsurg.2011.12.040.
43. Wilhelm JJ, Bellin MD, Dunn TB, et al. Proposed thresholds for pancreatic tissue volume for safe intraportal islet autotransplantation after total pancreatectomy. *Am J Transplant* 2013;13(12):3183–3191. doi:10.1111/ajt.12482
44. Kanak MA, Takita M, Kunnathodi F, et al. Inflammatory response in islet transplantation. *Int J Endocrinol* 2014;451035. doi:10.1155/2014/451035
45. Garcea G, Pollard CA, Illouz S, et al. Patient satisfaction and costeffectiveness following total pancreatectomy with islet cell transplantation for chronic pancreatitis. *Pancreas* 2013;42(2):322–328. doi:10.1097/MPA.0b013e318264d027.
46. Niederhaus SV, Kaufman DB, Odorico JS. Induction therapy in pancreas transplantation. *Transpl Int* 2013; 26:704–14.
47. Shapiro AM, Lakey JR, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med* 2000;343(4):230–238
48. Kitchens WH, Turgeon NA. Immunosuppression in Pancreas Transplantation: What Has Changed in 20 Years?. *Clin Transplant Rep* 2016; 3:154–60.
49. Calne RY, Rolles K, White DJ, et al. Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. *Lancet* 1979;2(8151):1033–1036.
50. Nielsen JH, Mandruppoulsen T, Nerup J. Direct effects of cyclosporine-a on human pancreatic betacells. *Diabetes* 1986;35(9):1049–1052.
51. Maffi P, Bertuzzi F, De Taddeo F, et al. Kidney function after islet transplant alone in type 1 diabetes: impact of immunosuppressive therapy on progression of diabetic nephropathy. *Diabetes Care* 2007;30(5):1150–1155
52. Pepper AR, Gala-Lopez B, Ziff O, et al. Current status of clinical islet transplantation. *World J Transplant* 2013;3(4):48–53.
53. Humar A, Ramcharan T, Kandaswamy R, et al. Technical failures after pancreas transplants: why grafts fail and the risk factors—a multivariate analysis. *Transplantation* 2004; 78:1188–92.
54. Burke GW 3rd, Vendrame F, Pileggi A, et al. Recurrence of autoimmunity following pancreas transplantation. *Curr Diab Rep* 2011;11(5):413–419.
55. Atwell TD, Gorman B, Larson TS, et al. Pancreas transplants: experience with 232 percutaneous US-guided biopsy procedures in 88 patients. *Radiology* 2004;231(3):845–849.
56. Drachenberg CB, Papadimitriou JC, Klassen DK, et al. Evaluation of pancreas transplant needle biopsy: reproducibility and revision of histologic grading system. *Transplantation* 1997;63(11):1579–1586.
57. Drachenberg CB, Torrealba JR, Nankivell BJ, et al. Guidelines for the diagnosis of antibody-mediated rejection in pancreas allografts—updated banff grading schema. *Am J Transplant* 2011;11(9):1792–1802. doi: 10.1111/j.1600-6143.2011.03670.x.
58. Drachenberg CB, Odorico J, Demetris AJ, et al. Banff schema for grading pancreas allograft rejection: working proposal by a multi-disciplinary international consensus panel. *Am J Transplant* 2008;8(6):1237–1249.
59. Munivenkatappa R, Papadimitriou J, Drachenberg CB. Accelerated pancreas allograft sclerosis due to allograft rejection. *Pathol Case Rev* 2012;17(6):229–235.
60. Papadimitriou JC, Drachenberg CB, Klassen DK, et al. Histologic grading scheme for pancreas allograft rejection: application in the differential diagnosis from other pathologic entities. *Transplant Proc* 1998;30(2):267.
61. Drachenberg CB, Klassen DK, Weir MR, et al. Islet cell damage associated with tacrolimus and cyclosporine: morphological features in pancreas allograft biopsies and clinical correlation. *Transplantation* 1999;68(3):396–402.