

BÖLÜM 11

İNSÜLİN ALERJİSİ VE DESENSİTİZASYONU



Gürğün Tuğçe VURAL SOLAK¹

GİRİŞ

Alerji immün sistemimizin normalde zararsız olarak bilinen maddelere karşı oluşturduğu aşırı duyarlılık reaksiyonlarıdır. Günümüzde alerjik hastalıkların sıklığı giderek artmaktadır ve insülin preparatlarına karşı da aşırı duyarlılık reaksiyonları tanımlanmıştır. Bu reaksiyonların şiddeti hafif lokal reaksiyonlardan hayatı tehdit edici anafilaksiye kadar değişkenlik gösterebilir. Diyabet yönetiminde yarattığı zorluklar açısından insülin alerjilerinin endokrinoloji ve alerji uzmanları arasındaki iş birliği ile yönetilmesinde fayda vardır çünkü insülin bağımlı hastalarda insülin alerjilerine hızlı tanı koyulması ve uygun yönetiminin yapılması hayati önem arz etmektedir.

EPİDEMİYOLOJİ

İnsan insülinine ve insülin analoglarına karşı alerjik reaksiyonların nadir olarak görülmesi nedeniyle geniş kapsamlı epidemiyolojik çalışmalar bulunmamaktadır. Ancak insidans oranlarının %0.1 ile %7.1 arasında olduğu belirtilmektedir (1-3).

İnsülinin geliştirilme basamaklarına değinmek gerekirse 1922’de iki Kanadalı bilim insanı hayvan pankreas adacık hücrelerinden insülini izole ederek gönüllü insanlara enjekte etmişlerdir, ancak yeterince saf insülin olmaması nedeniyle hastaların birinde enjeksiyon bölgesinde 7.5 santimetrelik kallus dokusu geliştiği

¹ Uzm. Dr., Ankara Atatürk Sanatoryum Eğitim ve Araştırma Hastanesi, İmmünoloji ve Alerji Hastalıkları Kliniği, g.tugcevural@hotmail.com



KAYNAKLAR

1. Fernandez L, Duque S, Montalban C, et al. Allergy to human insulin. *Allergy*. 2003;58(12):1317-1317. doi: 10.1046/j.1398-9995.2003.00324.x
2. Radermecker RP, Scheen A. Allergy reactions to insulin: effects of continuous subcutaneous insulin infusion and insulin analogues. *Diabetes/Metabolism Research and Reviews*. 2007;23(5):348-355. doi: 10.1002/dmrr.714
3. Ghazavi MK, Johnston GA. Insulin allergy. *Clinics in Dermatology*. 2011;29(3):300-305. doi: 10.1016/j.clindermatol.2010.11.009
4. Bliss M. The discovery of insulin. *The Discovery of Insulin*: University of Toronto Press; 2019. doi: 10.3138/9781442621480
5. Jersild M. INSULIN ZINC SUSPENSION: FOUR YEARS'EXPERIENCE. *The Lancet*. 1956;268(6951):1009-1013. doi: 10.1016/S0140-6736(56)90266-5
6. Scherthaner G. Immunogenicity and allergenic potential of animal and human insulins. *Diabetes Care*. 1993;16(Supplement_3):155-165. doi: 10.2337/diacare.16.3.155
7. Katsoyannis PG, Tometsko A, Zalut C. Insulin Peptides. XII. Human Insulin Generation by Combination of Synthetic A and B Chains1. *Journal of the American Chemical Society*. 1966;88(1):166-167. doi: 10.1021/ja00953a033
8. Heinzerling L, Raile K, Rochlitz H, et al. Insulin allergy: clinical manifestations and management strategies. *Allergy*. 2008;63(2):148-155. doi: 10.1111/j.1398-9995.2007.01567.x
9. Sola-Gazagnes A, Pecquet C, Radermecker R, et al. Successful treatment of insulin allergy in a type 1 diabetic patient by means of constant subcutaneous pump infusion of insulin. *Diabetes Care*. 2003;26(10):2961-2962. doi: 10.2337/diacare.26.10.2961
10. Hasselmann C, Pecquet C, Bismuth E, et al. Continuous subcutaneous insulin infusion allows tolerance induction and diabetes treatment in a type 1 diabetic child with insulin allergy. *Diabetes & Metabolism*. 2013;39(2):174-177. doi: 10.1016/j.diabet.2012.10.002
11. Pichler WJ. Drug hypersensitivity reactions: classification and relationship to T-cell activation. *Drug Hypersensitivity*: Karger Publishers; 2007:168-189. doi: 10.1159/000104199
12. Kawanami D, Ito T, Watanabe Y, et al. Successful control of a case of severe insulin allergy with liraglutide. *Journal of Diabetes Investigation*. 2013;4(1):94-96. doi: 10.1111/j.2040-1124.2012.00239.x
13. Chng H, Leong K, Loh K. Primary systemic allergy to human insulin: recurrence of generalized urticaria after successful desensitization. *Allergy*. 1995;50(12):984-987. doi: 10.1111/j.1398-9995.1995.tb02512.x
14. Grammer L. Insulin allergy. *Clinical reviews in allergy*. 1986;4(2):189-200. doi: 10.1007/BF02991108
15. Alvarez-Thull L, Rosenwasser LJ, Brodie TD. Systemic allergy to endogenous insulin during therapy with recombinant DNA (rDNA) insulin. *Annals of Allergy, Asthma & Immunology*. 1996;76(3):253-256. doi: 10.1016/S1081-1206(10)63436-9
16. Brange J, Andersen L, Laursen ED, et al. Toward understanding insulin fibrillation. *Journal of pharmaceutical Sciences*. 1997;86(5):517-525. doi: 10.1021/js960297s
17. Maislos M, Mead P, Gaynor D, Robbins D. The source of the circulating aggregate of insulin in type I diabetic patients is therapeutic insulin. *The Journal of Clinical Investigation*. 1986;77(3):717-723. doi: 10.1172/JCI112366
18. Velcovsky H, Federlin K. Insulin-specific IgG and IgE antibody response in type I diabetic subjects exclusively treated with human insulin (recombinant DNA). *Diabetes Care*. 1982;5(Supplement_2):126-128. doi: 10.2337/diacare.5.2.S126
19. Darmon P, Castera V, Koeppel M-C, et al. Type III allergy to insulin detemir. *Diabetes Care*. 2005;28(12):2980-2980. doi: 10.2337/diacare.28.12.2980-a
20. Heinzerling L, Adkinson N, Nathan D, et al. Hypersensitivity reactions to insulins.



- (23/04/2022 tarihinde https://www.uptodate.com/contents/hypersensitivity-reactions-to-insulins?search=insulin%20allergy&source=search_result&selectedTitle=1~8&usage_type=default&display_rank=1 adresinden erişilmiştir.)
21. Goldfine A, Kahn C. Insulin allergy and insulin resistance. *Current therapy in endocrinology and Metabolism*. 1994;5:461-464. doi: : 10.1080/00325481.1978.11714725
 22. Bodtger U, Witttrup M. A rational clinical approach to suspected insulin allergy: status after five years and 22 cases. *Diabetic Medicine*. 2005;22(1):102-106. doi: 10.1111/j.1464-5491.2004.01352.x
 23. Wheeler BJ, Taylor BJ. Successful management of allergy to the insulin excipient metacresol in a child with type 1 diabetes: a case report. *Journal of Medical Case Reports*. 2012;6(1):1-4. doi:10.1186/1752-1947-6-263
 24. Takata H, Kumon Y, Osaki F, et al. The human insulin analogue aspart is not the almighty solution for insulin allergy. *Diabetes Care*. 2003;26(1):253-254. doi: 10.2337/diacare.26.1.253
 25. Matheu V, Perez E, Hernández M, et al. Insulin allergy and resistance successfully treated by desensitisation with Aspart insulin. *Clinical and Molecular Allergy*. 2005;3(1):1-5. doi:10.1186/1476-7961-3-16
 26. Atik D, Büyükcım F, Yılmaz D, et al. Angioedema after the first dose of metformin. *The American Journal of Emergency Medicine*. 2013;31(3):634. e635. doi: 10.1016/j.ajem.2012.10.021
 27. Pérez E, Martínez-Tadeo J, Callero A, et al. A case report of allergy to exenatide. *The Journal of Allergy and Clinical Immunology. In Practice*. 2014;2(6):822-823. doi: 10.1016/j.jaip.2014.05.011
 28. Moyes V, Driver R, Croom A, et al. Insulin allergy in a patient with type 2 diabetes successfully treated with continuous subcutaneous insulin infusion. *Diabetic Medicine*. 2006;23(2):204-206. doi: 10.1111/j.1464-5491.2006.01811.x
 29. Näf S, Esmatjes E, Recasens M, et al. Continuous subcutaneous insulin infusion to resolve an allergy to human insulin. *Diabetes Care*. 2002;25(3):634-635. doi: 10.2337/diacare.25.3.634-a
 30. Asai M, Yoshida M, Miura Y. Immunologic tolerance to intravenously injected insulin. *New England Journal of Medicine*. 2006;354(3):307-309. doi: 10.1056/NEJMc052463
 31. Andrade P, Barros L, Gonçalves M. Type 1 Ig-E mediated allergy to human insulin, insulin analogues and beta-lactam antibiotics. *Anais Brasileiros de Dermatologia*. 2012;87:917-919. doi: 10.1590/S0365-05962012000600018
 32. Chu Y-Q, Cai L-J, Jiang D-C, Jia D, et al. Allergic shock and death associated with protamine administration in a diabetic patient. *Clinical Therapeutics*. 2010;32(10):1729-1732. doi: 10.1016/j.clinthera.2010.09.010
 33. Stewart WJ, McSweeney SM, Kellett MA, et al. Increased risk of severe protamine reactions in NPH insulin-dependent diabetics undergoing cardiac catheterization. *Circulation*. 1984;70(5):788-792. doi: 10.1161/01.CIR.70.5.788
 34. Weiss ME, Adkinson NF. Allergy to protamine. *Clinical Reviews in Allergy*. 1991;9(3):339-355. doi: 10.1007/BF02802312
 35. Weiss M, Chatham F, Kagey-Sobotka A, et al. Serial immunological investigations in a patient who had a life-threatening reaction to intravenous protamine. *Clinical & Experimental Allergy*. 1990;20(6):713-720. doi: 10.1111/j.1365-2222.1990.tb02713.x
 36. Porsche R, Brenner ZR. Allergy to protamine sulfate. *Heart & Lung*. 1999;28(6):418-428. doi: 10.1016/S0147-9563(99)70031-2
 37. Chang L-C, Liang JF, Lee H-F, et al. Low molecular weight protamine (LMWP) as nontoxic heparin/low molecular weight heparin antidote (II): in vitro evaluation of efficacy and toxicity. *Aaps Pharmsci*. 2001;3(3):15-23. doi: 10.1208/ps030318
 38. Roest M, Shaw S, Orton D. Insulin-injection-site reactions associated with type I latex allergy. *New England Journal of Medicine*. 2003;348(3):265-266. doi: 10.1056/NEJM200301163480320
 39. Heinzerling L, Mari A, Bergmann K-C, et al. The skin prick test–European standards. *Clinical and Translational Allergy*. 2013;3(1):1-10. doi:10.1186/2045-7022-3-3



40. Lee A-Y, Chey W-Y, Choi J, et al. Insulin-induced drug eruptions and reliability of skin tests. *Acta Dermato-Venereologica*. 2002;82(2):114-117. doi: 10.1080/00015550252948149
41. DeShazo RD, Mather P, Grant W, et al. Evaluation of patients with local reactions to insulin with skin tests and in vitro techniques. *Diabetes Care*. 1987;10(3):330-336. doi: 10.2337/diacare.10.3.330
42. Madero M, Sastre J, Carnes J, et al. IgG4-mediated allergic reaction to glargine insulin. *Allergy*. 2006;61(8):1022-1023. doi: 10.1111/j.1398-9995.2006.01117.x
43. Yuan T, Zhao W, Wang L, et al. Continuous subcutaneous insulin infusion as an effective method of desensitization therapy for diabetic patients with insulin allergy: a 4-year single-center experience. *Clinical Therapeutics*. 2016;38(11):2489-2494. doi: 10.1016/j.clinthera.2016.09.018
44. Wu P, Ji C, Wang M, et al. Desensitization of allergy to human insulin and its analogs by administering insulin aspart and insulin glargine. Paper presented at: *Annales d'endocrinologie*, 2013. doi: 10.1016/j.ando.2012.11.005
45. Yokoyama H, Fukumoto S, Koyama H, et al. Insulin allergy; desensitization with crystalline zinc-insulin and steroid tapering. *Diabetes Research and Clinical Practice*. 2003;61(3):161-166. doi: 10.1016/S0168-8227(03)00114-1
46. Eguíluz-Gracia I, Rodríguez-Álvarez M, Cimarra-Álvarez M, et al. Desensitization for insulin allergy: a useful treatment also for local forms. *Journal of Investigational Allergology & Clinical Immunology*. 2012;22(3):215-216.
47. Jutel M, Akdis M, Budak F, et al. IL-10 and TGF- β cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. *European journal of immunology*. 2003;33(5):1205-1214. doi: 10.1002/eji.200322919
48. Mattson JR, Patterson R, Roberts M. Insulin therapy in patients with systemic insulin allergy. *Archives of internal medicine*. 1975;135(6):818-821. doi: 10.1001/archinte.1975.00330060062008
49. Fujikawa T, Imbe H, Date M, et al. Severe insulin allergy successfully treated with continuous subcutaneous insulin infusion. *Diabetes Research and Clinical Practice*. 2012;97(2):e31-e33. doi: 10.1016/j.diabres.2012.04.027
50. Rojas J, Villalobos M, Martínez MS, et al. Successful management of insulin allergy and autoimmune polyendocrine syndrome type 4 with desensitization therapy and glucocorticoid treatment: a case report and review of the literature. *Case Reports in Immunology*. 2014;2014. doi: 10.1155/2014/394754
51. Jacquier J, Chik C, Senior P. A practical, clinical approach to the assessment and management of suspected insulin allergy. *Diabetic Medicine*. 2013;30(8):977-985. doi: 10.1111/dme.12194
52. Frigerio C, Aubry M, Gomez F, et al. Desensitization-resistant insulin allergy. *Allergy*. 1997;52(2):238-239. doi: 10.1111/j.1398-9995.1997.tb00988.x
53. Witters LA, Ohman JL, Weir GC, et al. Insulin antibodies in the pathogenesis of insulin allergy and resistance. *The American Journal of Medicine*. 1977;63(5):703-709. doi: 10.1016/0002-9343(77)90155-3
54. Cavelti-Weder C, Muggli B, Keller C, et al. Successful use of omalizumab in an inadequately controlled type 2 diabetic patient with severe insulin allergy. *Diabetes Care*. 2012;35(6):e41-e41. doi: 10.2337/dc12-0115
55. Yong PF, Malik R, Arif S, et al. Rituximab and omalizumab in severe, refractory insulin allergy. *New England Journal of Medicine*. 2009;360(10):1045-1047. doi: 10.1056/NEJMc0808282
56. Mandrup-Poulsen T, Mølvig J, Pildal J, et al. Leukocytoclastic vasculitis induced by subcutaneous injection of human insulin in a patient with type 1 diabetes and essential thrombocytemia. *Diabetes Care*. 2002;25(1):242-243. doi: 10.2337/diacare.25.1.242
57. Silva ME, Mendes MJ, Ursich MJ, et al. Human insulin allergy-immediate and late type III reactions in a long-standing IDDM patient. *Diabetes Research and Clinical Practice*. 1997;36(2):67-70. doi: 10.1016/S0168-8227(97)00031-4
58. Clerx V, Van Den Keybus C, Kochuyt A, et al. Drug intolerance reaction to insulin therapy caused by metacresol. *Contact Dermatitis*. 2003;48(3):162-163. doi: 10.1034/j.1600-0536.2003.00034.x