BÖLÜM **24**

DİYABETİN FARMAKOLOJİK TEDAVİSİNDE GÜNCEL YAKLAŞIMLAR

Şencay YILDIZ ŞAHİN[1]

GİRİŞ

Diabetes mellitus (DM), pankreasın yeterli insülin üretememesi ya da salgılanan insülinin etkin bir şekilde kullanamaması sonucu oluşan hiperglisemi ile seyreden ilerleyici kronik bir hastalıktır (1). Günümüzde, sıklığı ve kontrol altına alınamadığında yarattığı komplikasyonlar nedeniyle tüm dünyada ve ülkemizde giderek büyüyen toplum sağlığını tehdit eden global bir sorun olarak karşımıza çıkmaktadır. 2019 yılı itibari ile dünyada 463 milyon diyabet tanısı almış hasta sayısı varken, bu sayının 2030 yılında 578 milyona ulaşacağı tahmin edilmektedir (2). Bu hızlı artış beraberinde diyabet tedavisinde yeni arayışlara sebep olmaktadır. Bu hastalığı yönetebilmek için tüm dünyada her yıl çeşitli kılavuzlar yayımlanmaktadır. Bu bölümde diabetes mellitus tedavisinde uygulanan güncel farmakolojik tedavi yaklaşımlarına yer verilecektir.

DİYABET TEDAVİSİNDE GENEL YAKLAŞIMLAR

Diyabet tanısı konduktan sonra yapılması gerekenler; bireye göre ayarlanmış diyet ve egzersiz programı oluşturmak ve diyabet hastalığı hakkında bilgi ve eğitim vermektir. Bunun yanında optimal kan şeker kontrolünü sağlayabilmek için farmakolojik tedavi de sıklıkla kullanılır. Tedavide kullanılan birçok ajan mevcuttur ancak antidiyabetik tedavi seçimine; diyabetin tipine, hastanın yandaş hastalıklarına, kan şeker düzeyine, ilacın etkinliğine, ilaçların yan etkilerine, ilacın kilo üzerine etkisine ve maliyete göre bireysel bazda karar verilir (Tablo 1).

---

[1] Uzm. Dr., Haseki Eğitim ve Araştırma Hastanesi, Sağlık Bilimleri Üniversitesi, İç Hastalıkları Kliniği, drsencayyildiz@gmail.com

(47-52). Uzun etkili insülin analogları gece, akşam ya da sabah kullanılabilir. Özellikle çoklu insülin enjeksiyonu uygulayamayacak bazı hastalarda genellikle günde 2 doz karışım insülinde verilebilir.

Bazal insülin gereksinimi arttıkça (>0.5 IU/kg) tedavinin yoğunlaştırılması düşünülmelidir. Bunun için alternatif olarak bazal-bolus insülin tedavisi, bifazik insülin tedavisi veya GLP-1 analogları tedaviye eklenebilir. Hiperglisemi semptomları varsa öncelikle bazal-bolus insülin rejimine geçilmesi düşünülmelidir. Bolus insülin tedavisi postprandiyal kan glukoz düzeyini kontrol altına alır ve en yüksek olan öğünden başlayarak kademeli olarak artırılmak suretiyle tedaviye eklenir.

Özellikle kilo alma eğilimi olan obez hastalarda oral antihiperglisemik kombinasyonlar ile glisemi kontrolü sağlanamıyorsa metformin ve bazal insüline GLP-1 analogları veya SGLT-2 inhibitörleri eklenerek uygun bir kombinasyon tedavisi verilebilir.

Tip 2 diyabetli hastalarda; araya giren ciddi bir enfeksiyon, gebelik, akut metabolik dekompansasyon (diyabetik ketoasidoz), cerrahi veya diyabet komplikasyonlarının ilerlemesi gibi durumlarda hiç vakit kaybedilmeden erken dönemde bazal-bolus insülin tedavisi başlanmalıdır.

Bariatrik Cerrahi

Tip 2 diyabetli ve obezitesi olan seçilmiş hastalar için (vücut kitle indeksi [BKİ] ≥40 kg/m^2 olan veya BKİ ≥35 kg/m^2 olup medikal tedaviye rağmen optimal kan şeker kontrolü sağlanamayan hastalara) obezite cerrahisi önerilir (53,54). Bariyatrik cerrahi öncesi hastalar cerrahi endikasyonlar ve kontrendikasyonlar açısından ayrıntılı olarak değerlendirilmeli, hastaların uyum, istek ve kararlılık durumu belirlenmelidir.

KAYNAKLAR

1. Karuranga, S., Rocha Fernandes, J., Huang, Y., Malanda, B. (2017), *International Diabetes Federation Diabetes Atlas*, 8th Edition, (a) Chapter 1, What is diabetes? 16; (b) Chapter 3, Global picture, 40-41.
2. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. *Diabetes Res Clin Pract.* 2019;157 :107843. [Crossref]
3. American Diabetes Association Professional Practice Committee, Draznin B, Aroda VR, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. *Diabetes Care* 2022; 45:S125.

4. Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2021;44:2589–2625

5. Tricco AC, Ashoor HM, Antony J, et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. *BMJ* 2014;349:g5459

6. Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with Type 1 diabetes using a treat-totarget basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. *Diabet Med* 2008;25:442–449

7. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA* 2003;289:2254–2264

8. Russell-Jones D, Bode BW, De Block C, et al. Fast-acting insulin aspart improves glycemic control in basal-bolus treatment for type 1 diabetes: results of a 26-week multicenter, active-controlled, treat-to-target, randomized, parallel-group trial (onset 1). *Diabetes Care* 2017;40:943–950

9. Klaff L, Cao D, Dellva MA, et al. Ultra rapid lispro improves postprandial glucose control compared with lispro in patients with type 1 diabetes: results from the 26-week PRONTO-T1D study. *Diabetes Obes Metab* 2020;22: 1799–1807

10. Blevins T, Zhang Q, Frias JP, Jinnouchi H; PRONTO-T2D Investigators. Randomized doubleblind clinical trial comparing ultra rapid lispro with lispro in a basal-bolus regimen in patients with type 2 diabetes: PRONTO-T2D. *Diabetes Care* 2020;43:2991–2998

11. Bode BW, McGill JB, Lorber DL, Gross JL, Chang PC, Bregman DB; Affinity 1 Study Group. Inhaled technosphere insulin compared with injected prandial insulin in type 1 diabetes: a randomized 24-week trial. *Diabetes Care* 2015;38:2266–2273 10. Russell-Jones D, B

12. Lane W, Bailey TS, Gerety G, et al.; Group Information; SWITCH 1. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 1 diabetes: the SWITCH 1 randomized clinical trial. *JAMA* 2017;318:33–44

13. Home PD, Bergenstal RM, Bolli GB, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 1 diabetes: a randomized, phase 3a, open-label clinical trial (EDITION 4). *Diabetes Care* 2015;38:2217–2225

14. *Türkiye Endokrinoloji ve Metabolizma Derneği Diabetes Mellitus ve Komplikasyonlarının Tanı, Tedavi ve İzlem Kılavuzu-*2020

15. Pickup JC. The evidence base for diabetes technology: appropriate and inappropriate metaanalysis. *J Diabetes Sci Technol* 2013;7: 1567–1574

16. Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med* 2013;369:224–232

17. Buckingham BA, Raghinaru D, Cameron F, et al.; In Home Closed Loop Study Group. Predictive low-glucose insulin suspension reduces duration of nocturnal hypoglycemia in children without increasing ketosis. *Diabetes Care* 2015;38:1197–1204

18. Bell KJ, Smart CE, Steil GM, Brand-Miller JC, King B, Wolpert HA. Impact of fat, protein, and glycemic index on postprandial glucose control in type 1 diabetes: implications for intensive diabetes management in the continuous glucose monitoring era. *Diabetes Care* 2015;38:1008–1015

19. Whitehouse F, Kruger DF, Fineman M, et al. A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. *Diabetes Care* 2002;25:724–7303

20. Ratner RE, Want LL, Fineman MS, et al. Adjunctive therapy with the amylin analogue pramlintide leads to a combined improvement in glycemic and weight control in insulin-treated subjects with type 2 diabetes. *Diabetes Technol Ther* 2002;4:51–61

21. Hollander PA, Levy P, Fineman MS, et al. Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. *Diabetes Care* 2003;26:784–790

22. Ratner RE, Dickey R, Fineman M, et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in type 1 diabetes mellitus: a 1-year, randomized controlled trial. *Diabet Med* 2004;21:1204–1212

23. Meng H, Zhang A, Liang Y, Hao J, Zhang X, Lu J. Effect of metformin on glycaemic control in patients with type 1 diabetes: a meta-analysis of randomized controlled trials. *Diabetes Metab Res Rev* 2018;34:e2983

24. Petrie JR, Chaturvedi N, Ford I, et al.; REMOVAL Study Group. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2017;5:597–609

25. Dean PG, Kukla A, Stegall MD, Kudva YC. Pancreas transplantation. *BMJ* 2017;357:j1321

26. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018;41:2669–2701

27. Buse JB, Wexler DJ, Tsapas A, et al. 2019 update to: management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2020;43:487–493

28. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577–1589

29. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. Accessed 20 October 2021. Available from https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-revises-warnings-regarding-use-diabetes-medicine-metformin –certain

30. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2016; 375:1834.

31. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016; 375:311

32. Mann JFE, Ørsted DD, Brown-Frandsen K, et al. Liraglutide and Renal Outcomes in Type 2 Diabetes. *N Engl J Med* 2017; 377:839

33. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019; 394:121.

34. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. Lancet 2019; 394:131.

35. Kanie T, Mizuno A, Takaoka Y, et al. Dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists and sodium-glucose co-transporter-2 inhibitors for people with cardiovascular disease: a network meta-analysis. *Cochrane Database Syst Rev* 2021; 10:CD013650.

36. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med* 2020; 383:1436.

37. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2019; 380:347.

38. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015; 373:2117.

39. NeNeal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017; 377:644.

40. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med* 2019; 380:2295.

41. Shyangdan DS, Royle P, Clar C, et al. Glucagon-like peptide analogues for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2011; :CD006423.

42. Singh S, Wright EE Jr, Kwan AY, et al. Glucagon-like peptide-1 receptor agonists compared with basal insulins for the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Obes Metab 2017*; 19:228.

43. American Diabetes Association Professional Practice Committee, Draznin B, Aroda VR, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. *Diabetes Care* 2022; 45:S125.

44. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018; 41:2669.

45. Buse JB, Wexler DJ, Tsapas A, et al. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2020; 43:487.

46. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. *Diabetes Care* 2012; 35:2650.

47. Rubino F, Nathan DM, Eckel RH, et al. Metabolic Surgery in Type 2 Diabetes Treatment Algorithm: Joint Statement from International Diabetes Organizations. *Diabetes Care* 2016; 39:861.

48. American Diabetes Association Professional Practice Committee, Draznin B, Aroda VR, et al. 8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Medical Care in Diabetes-2022. *Diabetes Care* 2022; 45:S113.

49. Singh SR, Ahmad F, Lal A, Yu C, Bai Z, Bennett H. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. *CMAJ* 2009;180:385–397

50. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2007;2:CD005613

51. Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: a meta-analysis. *Diabetes Res Clin Pract* 2008;81:184–189

52. Owens DR, Traylor L, Mullins P, Landgraf W. Patient-level meta-analysis of efficacy and hypoglycaemia in people with type 2 diabetes initiating insulin glargine 100U/mL or neutral protamine Hagedorn insulin analyzed according to concomitant oral antidiabetes therapy. *Diabetes Res Clin Prac*t 2017;124(Suppl. C):57–65

53. Riddle MC, Rosenstock J; Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003;26:3080–3086

54. Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose- lowering drugs in insulin-naive people with type 2 diabetes. *Diabetes Care* 2006;29:1269–1274