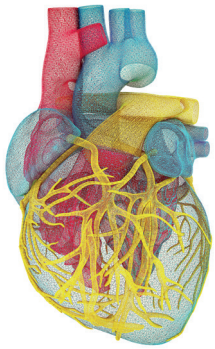

BÖLÜM **49**

Diyabetik Hastada Kronik Böbrek Hastalığı

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GİRİŞ

Diyabetik böbrek hastalığı (nefropati), idrarda patolojik düzeyde protein(albümin) kaybı, diyabetik glomeruler lezyonlar ve GFR azalışı ile karakterize bir diyabet komplikasyonudur. Bu mikrovaskuler komplikasyon, kronik böbrek yetmezliği ve son dönem böbrek yetmezliğinin en sık ve önemli nedeni olmakla birlikte; Tip 1 diyabetli hastaların yaklaşık %30'unda, Tip 2 diyabetli hastaların yaklaşık %40'ında hastalık seyrinde gelişmektedir (1).

Diyabetik nefropati gelişimi için başlıca modifiye edilebilir riskler hiperglisemi, hipertansiyon ve dislipidemidir (2). Ayrıca sigara içimi de diyabetik nefropati için güçlü bir risk faktörü olarak kabul edilmektedir (3). İleri yaş, cinsiyet (erkekler daha yatkın), ırk(Afrikalı Amerikalılar, Meksikalı Amerikalılar ve Pima Kızılderelileri daha yatkın) modifiye edilemeyen risk faktörlerindendir. Ek olarak aile öyküsü olanlarda nefropati gelişimi riski daha yüksektir. (4, 5)

Yapısal Değişiklikler ve Patoloji

Diyabetik nefropatide böbrekte yapısal ve fonksiyonel değişiklikler meydana gelmektedir. En erken değişiklik glomerular bazal membran kalınlaşması olup Tip 1 diyabet tanısından sonraki ilk 1,5-2 yıl içinde gerçekleşmektedir. Hastalık ilerledikçe mesangial genişleme ve karakteristik bir bulgu olan noduler glomeruloskleroz (Kimmelstiel-Wilson nodülleri) de gözlenir. Erken dönemde tübüler hipertrofi mevcut olup ilerleyen dönemlerde interstisyel fibrosis, tübüler atrofi ve arteriolar hyalinosis de gelişir. Daha ileri durumlarda makrofaj ve T lenfosit infiltrasyonu gerçekleşir. Ayrıca podosit kaybı ve endotel hücre fenestrasyonunda azalma gözlenir (6). Fonksiyonel olarak ise erken dönemde glomerular hiperfiltrasyon ve artmış albumin atılımı saptanırken; hastalık progrese oldukça nefropati, proteinüride artış ve GFR'de düşüş gözlenmektedir (1). (Tablo 1'de diyabetik nefropatide görülen patolojik değişikliklerin uluslararası sınıflandırılması verilmiştir.)

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hasar riski vardır. Glomerular hiperfiltrasyon, inflamasyon ve fibrosis mekanizmalarını hedefleyen yeni ajanlar, yeni tedavilerin odak noktası olmuştur. Ruboxistaurin (protein C kinaz-beta inhibitörü, barisitinib (selektif Janus kinaz-1 ve 2 inhibitörü), pentoksifilin (anti-inflamatuar ve antifibrotik ajan) ve atrasentan (selektif endotelin-A reseptör antagonisti) umut vadeden ajanlardır (7, 40, 49-51). Bununla birlikte, bu ajanların hiçbiri henüz kullanım onayı almamıştır.

KAYNAKLAR

1. Lim A. Diabetic nephropathy - complications and treatment. *Internal Journal of Nephrology and Renovascular Disease* 2014;7:361-81.
2. Rossing P, Hougaard P, Parving HH. Risk factors for development of incipient and overt diabetic nephropathy in type 1 diabetic patients: a 10-year prospective observational study. *Diabetes Care.* 2002;25(5):859-64.
3. Scott LJ, Warram JH, Hanna LS, et al. A nonlinear effect of hyperglycemia and current cigarette smoking are major determinants of the onset of microalbuminuria in type 1 diabetes. *Diabetes.* 2001;50(12):2842-9.
4. Satko SG, Langefeld CD, Daeihagh P, et al. Nephropathy in siblings of African Americans with overt type 2 diabetic nephropathy. *American Journal of Kidney Diseases.* 2002;40(3):489-94.
5. Pettitt DJ, Saad MF, Bennett PH, et al. Familial predisposition to renal disease in two generations of Pima Indians with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia.* 1990;33(7):438-43.
6. Weil EJ, Lemley KV, Mason CC, et al. Podocyte detachment and reduced glomerular capillary endothelial fenestration promote kidney disease in type 2 diabetic nephropathy. *Kidney International.* 2012;82(9):1010-7.
7. Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. *Clinical Journal of the American Society of Nephrology.* 2017;12(12):2032-45.
8. Rudberg S, Rasmussen LM, Bangstad HJ, et al. Influence of insertion/deletion polymorphism in the ACE-I gene on the progression of diabetic glomerulopathy in type 1 diabetic patients with microalbuminuria. *Diabetes Care.* 2000;23(4):544-8.
9. Ha H, Lee HB. Reactive oxygen species as glucose signaling molecules in mesangial cells cultured under high glucose. *Kidney International Supplements.* 2000;77:S19-25.
10. Srivastava SK, Ramana KV, Bhatnagar A. Role of aldose reductase and oxidative damage in diabetes and the consequent potential for therapeutic options. *Endocrine Reviews.* 2005;26(3):380-92.
11. Sheetz MJ, King GL. Molecular understanding of hyperglycemia's adverse effects for diabetic complications. *Jama.* 2002;288(20):2579-88.
12. Derubertis FR, Craven PA. Activation of protein kinase C in glomerular cells in diabetes. Mechanisms and potential links to the pathogenesis of diabetic glomerulopathy. *Diabetes.* 1994;43(1):1-8.
13. Schmid H, Boucherot A, Yasuda Y, et al. Modular activation of nuclear factor-kappaB transcriptional programs in human diabetic nephropathy. *Diabetes.* 2006;55(11):2993-3003.
14. Mudaliar H, Pollock C, Komala MG, et al. The role of Toll-like receptor proteins (TLR) 2 and 4 in mediating inflammation in proximal tubules. *American Journal of Physiology-Renal Physiology.* 2013;305(2):F143-54.
15. Lim AK, Tesch GH. Inflammation in diabetic nephropathy. *Mediators of Inflammation.* 2012;2012:146154.
16. Furuta T, Saito T, Ootaka T, et al. The role of macrophages in diabetic glomerulosclerosis. *American Journal of Kidney Diseases.* 1993;21(5):480-5.
17. Moriya R, Manivel JC, Mauer M. Juxtaglomerular apparatus T-cell infiltration affects glomerular structure in Type 1 diabetic patients. *Diabetologia.* 2004;47(1):82-8.
18. Eller K, Kirsch A, Wolf AM, et al. Potential role of regulatory T cells in reversing obesity-linked insulin resistance and diabetic nephropathy. *Diabetes.* 2011;60(11):2954-62.
19. National Kidney Foundation, KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. *American Journal of Kidney Diseases.* 2012;60(5):850-86.
20. Gall MA, Hougaard P, Borch-Johnsen K, et al. Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: prospective, observational study. *Bmj.* 1997;314(7083):783-8.
21. Bruno G, Merletti F, Biggeri A, et al. Progression to overt nephropathy in type 2 diabetes: the Casale Monferrato Study. *Diabetes Care.* 2003;26(7):2150-5.
22. Molitch ME, DeFronzo RA, Franz MJ, et al. Nephropathy in diabetes. *Diabetes Care.* 2004;27 Suppl 1:S79-83.
23. Williamson JR, Chang K, Frangos M, et al. Hyperglycemic pseudohypoxia and diabetic complications. *Diabetes.* 1993;42(6):801-13.
24. Moseley KF. Type 2 diabetes and bone fractures. *Current Opinion in Endocrinology, Diabetes and Obesity.* 2012;19(2):128-35.
25. Draznin B, Aroda VR, Bakris G, et al. Chronic Kidney Disease and Risk Management: Standards of Medical Care in Diabetes-2022. *Diabetes Care.* 2022;45(Suppl 1):S175-s84.
26. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. *Diabetes Care.* 2014;37(10):2864-83.
27. de Boer IH, Sun W, Cleary PA, et al. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *The New England Journal of Medicine.* 2011;365(25):2366-76.
28. Zoungas S, Arima H, Gerstein HC, et al. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled tri-

als. *Lancet Diabetes and Endocrinology*. 2017;5(6):431-7.
29. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *The New England Journal of Medicine.* 2008;358(24):2545-59.
30. Papademetriou V, Lovato L, Doumas M, et al. Chronic kidney disease and intensive glycemic control increase cardiovascular risk in patients with type 2 diabetes. *Kidney International.* 2015;87(3):649-59.
31. Heerspink HJ, Desai M, Jardine M, et al. Canagliflozin Slows Progression of Renal Function Decline Independently of Glycemic Effects. *Journal of the American Society of Nephrology.* 2017;28(1):368-75.
32. Zelniker TA, Braunwald E. Cardiac and Renal Effects of Sodium-Glucose Co-Transporter 2 Inhibitors in Diabetes: JACC State-of-the-Art Review. *Journal of the American College of Cardiology.* 2018;72(15):1845-55.
33. Yaribeygi H, Butler AE, Atkin SL, et al. Sodium-glucose cotransporter 2 inhibitors and inflammation in chronic kidney disease: Possible molecular pathways. *Journal of Cellular Physiology.* 2018;234(1):223-30.
34. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *The New England Journal of Medicine.* 2016;375(4):311-22.
35. Mann JFE, Ørsted DD, Brown-Frandsen K, et al. Liraglutide and Renal Outcomes in Type 2 Diabetes. *The New England Journal of Medicine.*2017;377(9):839-48.
36. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. *JAMA Cardiology.* 2021;6(2):148-58.
37. Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the Effects of Glucagon-Like Peptide Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus. *Circulation.* 2019;139(17):2022-31.
38. Emdin CA, Rahimi K, Neal B, et al. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *Jama.* 2015;313(6):603-15.
39. de Boer IH, Bangalore S, Benetos A, et al. Diabetes and Hypertension: A Position Statement by the American Diabetes Association. *Diabetes Care.* 2017;40(9):1273-84.
40. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *The New England Journal of Medicine.* 1993;329(20):1456-62.
41. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *The New England Journal of Medicine.* 2001;345(12):851-60.
42. Wu HY, Peng CL, Chen PC, et al. Comparative effectiveness of angiotensin-converting enzyme inhibitors versus angiotensin II receptor blockers for major renal outcomes in patients with diabetes: A 15-year cohort study. *PLoS One.* 2017;12(5):e0177654.
43. Weil EJ, Fufaa G, Jones LI, et al. Effect of losartan on prevention and progression of early diabetic nephropathy in American Indians with type 2 diabetes. *Diabetes.* 2013;62(9):3224-31.
44. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *The New England Journal of Medicine.* 2009;361(1):40-51.
45. Bangalore S, Fakheri R, Toklu B, et al. Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials. *Bmj.* 2016;352:i438.
46. Haller H, Ito S, Izzo JL, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *The New England Journal of Medicine.* 2011;364(10):907-17.
47. de Boer IH, Khunti K, Sadusky T, et al. Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Diabetes Care.* 2022.
48. Bakris GL, Agarwal R, Anker SD, et al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. *The New England Journal of Medicine.* 2020;383(23):2219-29.
49. Brosius FC, Tuttle KR, Kretzler M. JAK inhibition in the treatment of diabetic kidney disease. *Diabetologia.* 2016;59(8):1624-7.
50. Navarro-González JF, Mora-Fernández C, Muros de Fuentes M, et al. Effect of pentoxifylline on renal function and urinary albumin excretion in patients with diabetic kidney disease: the PREDIAN trial. *Journal of the American Society of Nephrology.* 2015;26(1):220-9.
51. Heerspink HJL, Parving HH, Andress DL, et al. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. *Lancet.* 2019;393(10184):1937-47.