

BÖLÜM 23

ÇOCUK VE ADOLESANLARDA DİYABETİK BÖBREK HASTALIĞI



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TANIM

Diabetes mellitus (DM), insanları etkileyen en yaygın metabolik bozukluktur. Pankreas β hücrelerinin immün harabiyetine bağlı insülin üretim kusurundan kaynaklanan tip 1 diabetes mellitus (DM1), periferik insülin direncinden kaynaklanan tip 2 diabetes mellitus (DM2) ya da her ikisinin kombinasyonu şeklinde görülebilir. DM, yaşam kalitesini bozan mikrovasküler komplikasyonlara yol açabilir (1,2).

Diabetik böbrek hastalığı (DBH) veya diabetik nefropati, diabetes mellitusun sinsi ve en sık görülen mikrovasküler komplikasyonlarından biridir. Mikroalbuminüri (MA) DBH'nin bilinen en iyi belirteçlerinden biridir (2). Hastalık mikroalbuminüri ile başlayıp son dönem böbrek yetmezliğine kadar ilerleyebilir. Bu nedenle, mikroalbuminürinin taranması ve erken tespiti nefropatinin ve aşikar proteinürinin önlenmesi için gereklidir.

EPİDEMİYOLOJİ

DBH, Amerika Birleşik Devletleri'ndeki yetişkinlerde SDBY'nin %60.6 oranı ile en sık nedeni olmasına rağmen çocuklarda ve ergenlerde daha nadirdir (3). DM1 tanısı alındıktan 20 yıl sonra hastaların yaklaşık olarak %30-40'ında nefropati gelişmekte olduğu, nefropatiyi takibinde 10 yıl sonra böbrek yetmezliği geliştiği bildirilmiştir (4). Alman Diyabet Dokümantasyon Sistemi'nin verileri, DM1'li

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pediatrik hastalarda dislipideminin tedavisi genelde ailesel hiperkolesterolemili çocuklarda yapılan denemelerin sonuçlarına dayanmaktadır (73).

Diyet : Mevcut bakım kriterleri içinde karbonhidrat sayımı, kalori takibi ve düşük glisemik indeksli gıdaların tüketimi gibi diyet eğitimi (17) ve glisemik kontrol ile ilişkili olarak artan fiziksel aktivitenin teşviki (74) bulunmaktadır. Ancak, DM2'li ergenlerin yalnızca %20-30'u yüksek yağlı besinleri sınırlar ve karbonhidrat sayımını kullanır (74). Amerikan Diyabet Derneği (ADA) kılavuzları da özellikle DM2'li gençler için kilo kontrolü önermektedir (17). Yakın zamanda, DiRECT'in (Diabetes Remission Clinical Trial) kayda değer başarısı, özellikle çok düşük enerjili diyetlerin (VLED) kullanımıyla diyabet yönetimine yönelik diyet yaklaşımını yeniden gündeme getirmiştir. Yeni tanılı DM2'li obez yetişkinler, 3-5 ay boyunca çok düşük kalorili (825-835 kcal/gün) bir diyet ile beslenmiş, ardından gıda ve aylık destek yeniden sağlanmış, ve sonuçta 12 ayda %46 ve 24 ayda %36 oranında diyabet remisyon oranı elde edilmiştir (75). Yakın tarihli bir metaanalizde çocuklarda ve ergenlerde VLED'ler birkaç uyarıyla birlikte kilo kaybı ve iyileştirilmiş kardiyometabolik sonuçları göstermiştir ancak VLED güvenliği değerlendirilememiştir (76).

KAYNAKLAR

1. Demirel F, Tepe D, Kara Ö, ve ark. Microvascular complications in adolescents with type 1 diabetes mellitus. *Journal of Clinical Research in Pediatric Endocrinology*. 2013; 5:3:145-9.
2. Najafian B, Mauer M. Progression of diabetich nephropathy in type 1 diabetich patients. *Diabetes Res Clin Pract*. 2009;83:1:1-8.
3. US Renal Data System. Annual Data Report: 2022 Available at: <https://adr.usrds.org>.
4. United States Renal Data System. USRDS 2018 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. National Institutes of Health. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda.
5. Raile K, Galler A, Hofer S, et al. Diabetic nephropathy in 27,805 children, adolescents, and adults with type 1 diabetes: Effect of diabetes duration, A1C, hypertension, dyslipidemia, diabetes onset, and sex. *Diabetes Care*. 2007;30:2523-28.
6. Salgado PP, Silva IN, Vieira EC, et al. Risk factors for early onset of diabetic nephropathy in pediatric type 1 diabetes. *J Pediatr Endocrinol Metab*. 2010; 23:1311-20.
7. Finne P, Reunanen A, Stenman S, et al. Incidence of end-stage renal disease in patients with type 1 diabetes. *JAMA*. 2005; 294:1782-7.
8. Maahs DM, Snively BM, Bell RA, et al. Higher prevalence of elevated albumin excretion in youth with type 2 than type 1 diabetes. The SEARCH for Diabetes in Youth Study. *Diabetes Care*. 2007; 30:2593-8.



9. Ogugua CF, Chikani UN, Ibekwe MU, et al. Early signs of microvascular complications in pediatric patients with short duration of type 1 diabetes mellitus seen in Southeast Nigeria. *Annals of African Medicine*. 2019; 18:4:200–5.
10. Marshall SL, Edidin DV, Arena VC, et al. Glucose control in Rwandan youth with type 1 diabetes following establishment of systematic, HbA1c based, care and education. *Diabetes Research and Clinical Practice*. 2015; 107:1:113–22.
11. Ahmed H. Elshaikh T. Abdullah M. Early Diabetic Nephropathy and Retinopathy in Patients with Type 1 Diabetes Mellitus Attending Sudan Childhood Diabetes Centre. *Journal of Diabetes Research*. 2020; Article ID:7181383:8.
12. Donaghue K.C. Marcovecchio M. Wadwa R. et al. ISPAD Clinical Practice Consensus Guidelines 2018 microvascular and macrovascular complications in children and adolescents. *Pediatric Diabetes*. 2018; 19:262–74.
13. Kher K. and Snyder MM. Kidney disease associated with diabetes mellitus and metabolic syndrome. Kher K.K. Schnaper H.W. Greenbaum L.A.(Eds) *Clinical Pediatric Nephrology* (3rd ed., pp. 533–40) 2017; CRC Press Taylor & Francis Group.
14. KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. *Am J Kidney Dis*. 2007; 49:2:12–154.
15. Afkarian M. Diabetic kidney disease in children and adolescents. *Pediatr Nephrol*. 2015; 30(1):65–74. doi: 10.1007/s00467-014-2796-5.
16. Eppens M, Craig M, Cusumano J, et al. Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. *Diabetes Care*. 2016; 29:1300–6.
17. American Diabetes Association. 13. Children and Adolescents: Standards of Medical Care in Diabetes-2021. *Diabetes Care*. 2021; 44:S180–99.
18. Gohda T, Niewczas M, Ficociello L, et al. Circulating TNF receptors 1 and 2 predict stage 3 CKD in type 1 diabetes. *J Am Soc Nephrol*. 2012; 23:16–524.
19. Sabbiseti V, Waikar S, Antoine D, et al. Blood kidney injury molecule-1 is a biomarker of acute and chronic kidney injury and predicts progression to ESRD in type I diabetes. *J Am Soc Nephrol*. 2014; 25:2177–86.
20. Hsu C, Xie D, Waikar S, et al. Urine biomarkers of tubular injury do not improve on the clinical model predicting chronic kidney disease progression. *Kidney Int*. 2017; 91:196–203.
21. Mamilly L, Mastrandrea LD, Vasquez CM, et al. Evidence of Early Diabetic Nephropathy in Pediatric Type 1 Diabetes. *Frontiers in Endocrinology*. 2021; Vol:12:Article:669954.
22. Burlaka L. Maidannyk V. Early functional and metabolic disorders in children with type 1 diabetes mellitus and diabetic nephropathy. *Pediatr Endocrinol Diabetes Metab*. 2021; 27(3):170-7.
23. Amin R, Widmer B, Prevost AT, et al. Risk of microalbuminuria and progression to macroalbuminuria in a cohort with childhood onset type 1 diabetes: prospective observational study. *BMJ*. 2008; 336: 697–701.
24. Perkins BA, Ficociello LH, Silva KH, et al. Regression of microalbuminuria in type 1 diabetes. *N Engl J Med*. 2003; 348: 2285–2293.
25. Kumar P, Krishna P, Reddy SC, et al. Incidence of type 1 diabetes mellitus and associated complications among children and young adults: results from Karnataka Diabetes Registry 1995–2008. *Journal of the Indian Medical Association*. 2008; 106:708–11.
26. Rossing P, Hougaard P, Parving H. 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: 859–64.



27. Torbjörnsdotter TB, Jaremkö GA, Berg UB. Ambulatory blood pressure and heart rate in relation to kidney structure and metabolic control in adolescents with Type I diabetes. *Diabetologia*. 2001; 44:865–73.
28. Gross JL, de Azevedo MJ, Silveiro SP, et al. Diabetic nephropathy: diagnosis, prevention, and treatment. *Diabetes Care*. 2005; 28:164–76.
29. Lurbe E, Redon J, Kesani A, et al. Increase in Nocturnal Blood Pressure and Progression to Microalbuminuria in Type 1 Diabetes. *N Engl J Med*. 2002; 347:797–805.
30. Marcovecchio ML, Dalton RN, Swarze CP, et al. Ambulatory blood pressure measurements are related to albumin excretion and are predictive for risk of microalbuminuria in young people with type 1 diabetes. *Diabetologia*. 2009; 52:1173–81.
31. Hovind P, Tarnow L, Rossing P, et al. Predictors for the development of microalbuminuria and macroalbuminuria in patients with type 1 diabetes: inception cohort study. *BMJ*: 2004; 328:1105–6.
32. Schultz CJ, Amin R, Dunger DB. Markers of microvascular complications in insulin dependent diabetes. *Arch Dis Child*. 2002; 87(1):10–2.
33. Schultz CJ, Konopelska-Bahu T, Dalton RN, et al. Microalbuminuria prevalence varies with age, sex, and puberty in children with type 1 diabetes followed from diagnosis in a longitudinal study. Oxford Regional Prospective Study Group. *Diabetes Care*. 1999; 22(3):495–502.
34. Weidmann P, Boehlen LM, de Courten M. Effects of different antihypertensive drugs on human diabetic proteinuria. *Nephrol Dial Transplant*. 1993; 8:582–4.
35. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin converting enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med*. 1993; 329:1456–62.
36. Pedrini MT, Levey AS, Lau J, et al. The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. *Ann Intern Med*. 1992; 124(7): 627–32.
37. Sale MM, Freedman BI. Genetic determinants of albuminuria and renal disease in diabetes mellitus. *Nephrol Dial Transplant*. 2006; 21(1):13–6.
38. Pezzolesi MG, Poznik GD, Mychaleckyj JC, et al. Genome-wide association scan for diabetic nephropathy susceptibility genes in type 1 diabetes. *Diabetes*. 2009; 58:1403–10.
39. Fagot-Campagna A, Pettitt DJ, Engelgau M, et al. Type 2 diabetes among North American children and adolescents: An epidemiologic health perspective. *J Pediatr*. 2000; 136:664–72.
40. Rossing P. The changing epidemiology of diabetic microangiopathy in type 1 diabetes. *Diabetologia*. 2005; 48(8):1439–44.
41. Borchers AT, Uibo R, Gershwin M, et al. The geoeidemiology of type 1 diabetes. *Autoimmunity Reviews*. 2010; 9:5:355–65.
42. Bjornstad P, Laffel L, Lynch J, et al. Elevated Serum Uric Acid Is Associated With Greater Risk for Hypertension and Diabetic Kidney Diseases in Obese Adolescents With Type 2 Diabetes: An Observational Analysis From the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) Study. *Diabetes Care*. 2019; 42:1120–8.
43. Sifuentes-Franco S, Padilla-Tejeda DE, Carrillo-Ibarra S, et al. Oxidative Stress, Apoptosis, and Mitochondrial Function in Diabetic Nephropathy. *Int J Endocrinol*. 2018; 1875870. doi: 10.1155/2018/1875870.
44. Vallon V, Komers R. Pathophysiology of the diabetic kidney. *Compr Physiol*. 2011; 1:1175–232.



45. Noh H, King GL. The role of protein kinase C activation in diabetic nephropathy. *Kidney Int.* 2007; 106:49–53.
46. Susztak K, Raff A, Schiffer M, et al. Glucose-induced reactive oxygen species cause apoptosis of podocytes. *Diabete.* 2006; 55:225–33.
47. Welsh GI, Hale LJ, Eremina V, et al. Insulin signaling to the glomerular podocyte is critical for normal kidney function. *Cell Metab.* 2010; 12:329–40.
48. Peti-Peterdi J, Gevorgyan H, Lam L, et al. Metabolic control of renin secretion. *Pflugers Archiv.* 2013; 465:53–8.
49. Bjornstad P, Nehus E, El Ghormli L, et al. Insulin Sensitivity and Diabetic Kidney Disease in Children and Adolescents With Type 2 Diabetes: An Observational Analysis of Data From the TODAY Clinical Trial. *Am J Kidney Dis.* 2018; 71:65–74.
50. Tonneijck L, Muskiet M, Smits M, et al. Glomerular Hyperfiltration in Diabetes: Mechanisms, Clinical Significance, and Treatment. *J Am Soc Nephrol.* 2017; 28:1023–39.
51. Cohen-Tervaert TW, Mooyaart AL, Amann K, et al. Renal Pathology Society. Pathologic classification of diabetic nephropathy. *J Am Soc Nephrol.* 2010; 21:556–63.
52. Frazer FL, Palmer LJ, Clarey A, et al. Relationship between renal volume and increased albumin excretion rates in children and adolescents with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab.* 2001; 14:875–81.
53. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. *J Pediatr.* 1994; 125:177–88.
54. The DCCT/EDIC Research Group: Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med.* 2011; 365:2366–76.
55. Perkovic V, Heerspink HL, Chalmers J, et al. ADVANCE Collaborative Group. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. *Kidney Int.* 2013; 83:517–23.
56. American Diabetes Association 9. Pharmacologic Approaches to Glycemic Treatment: standards of Medical Care in Diabetes-2021. *Diabetes Care.* 2021; 44:111–24.
57. Williams D, Nawaz A, Evans M. Renal Outcomes in Type 2 Diabetes: a Review of Cardiovascular and Renal Outcome Trials. *Diabetes Ther.* 2020; 11:369–86.
58. ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A metaanalysis of individual patient data. *Ann Intern Med.* 2001; 134:370–9.
59. Parving HH, Hommel E, Jensen BR, et al. Longterm beneficial effect of ACE inhibition on diabetic nephropathy in normotensive type 1 diabetic patients. *Kidney Int.* 2001; 60:228–34.
60. Bilous R, Chaturvedi N, Sjolie AK, et al. Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes: Three randomized trials. *Ann Intern Med.* 2009; 151:11–20.
61. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med.* 2009; 361:40–51.
62. Hirst JA, Taylor KS, Stevens RJ, et al. The impact of renin-angiotensin-aldosterone system inhibitors on type 1 and type 2 diabetic patients with and without early diabetic nephropathy. *Kidney Int.* 2012; 81:674–83.
63. National Kidney Foundation. KDOQI clinical practice guidelines for diabetes and CKD: 2012 Update. *Am J Kidney Dis.* 2012; 60:850–86.



64. Jennings DL, Kalus JS, Coleman CI, et al. Combination therapy with an ACE inhibitor and an angiotensin receptor blocker for diabetic nephropathy: A meta-analysis. *Diabet Med.* 2007; 24:486–93.
65. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med.* 2012; 369:1892–903.
66. Parving H-H, Persson F, Lewis JB, et al. AVOID Study Investigators. Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med.* 2008; 358:2433–46.
67. TODAY Study Group. Rapid rise in hypertension and nephropathy in youth with type 2 diabetes: the TODAY clinical trial. *Diabetes Care.* 2013; 36:1735–41.
68. Flynn J, Kaelber D, Baker-Smith C, et al. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. *Pediatrics.* 2017; 140(3):e20171904
69. Nosadini R, Tonolo G. Cardiovascular and renal protection in type 2 diabetes mellitus: The role of calcium channel blockers. *J Am Soc Nephrol.* 2002; 13(Suppl 3):216–23.
70. Kershner AK, Daniels SR, Imperatore G, et al. Lipid abnormalities are prevalent in youth with type 1 and type 2 diabetes: The SEARCH for Diabetes in Youth Study. *J Pediatr.* 2006; 149:314–9.
71. Reh CM, Mittelman SD, Wee CP, et al. A longitudinal assessment of lipids in youth with type 1 diabetes. *Pediatr Diabetes.* 2011; 12:365–71.
72. Marcovecchio ML, Dalton RN, Prevost AT, et al. Prevalence of abnormal lipid profiles and the relationship with the development of microalbuminuria in adolescents with type 1 diabetes. *Diabetes Care.* 2009; 32(4):658–63.
73. Avis HJ, Vissers MN, Stein EA, et al. A systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol.* 2007; 27(8): 1803–10.
74. Sauder K, Stafford J, The N, et al. Dietary strategies to manage diabetes and glycemic control in youth and young adults with youth-onset type 1 and type 2 diabetes: the SEARCH for diabetes in youth study. *Pediatr Diabetes.* 2020; 21:1093–101.
75. Lean M, Leslie W, Barnes A, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol* 2019; 7:344–55.
76. Andela S, Burrows T, Baur L, et al. Efficacy of very low-energy diet programs for weight loss: a systematic review with meta-analysis of intervention studies in children and adolescents with obesity. *Obes Rev.* 2019; 20:871–82.