

## Bölüm 21

# PERİFERİK DİYABETİK NÖROPATİ HASTASINDA YAKLAŞIM ve YÖNETİM

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### GİRİŞ

Periferik ve otonom sinir sistemlerinin tutulumu muhtemelen diyabetin en sık görülen komplikasyonudur. Klinik diyabetik nöropati, birçok örtüşme sendromu oluşmasına rağmen, nörolojik dağılıma göre farklı sendromlar şeklinde sınıflandırılır. Hem tip 1 hem de tip 2 diyabette nöropati prevalansı, hipergliseminin şiddeti ve süresine göre değişir. Simetrik polinöropati, otonom nöropati, radikülopati, mononöropati ve mononöropati multipleks gibi birçok diyabetik nöropati formları bulunmaktadır. Periferik ve otonom nöropatiler, diabetes mellituslu hastalarda en önemli morbidite nedenidir. Diyabetik periferik nöropatinin tanısında semptom ve bulgular ve sinir ileti çalışmaları birlikte değerlendirilmelidir. Elektromiyografi (EMG) sinir ileti çalışmalarında en sık kullanılan ve en duyarlı yöntemdir. Diyabetik periferik nöropatide tedavinin üç temel bileşeni glisemik kontrol, ayak bakımı ve ağrı tedavisidir (1).

### VAKA

61 yaşında erkek . Yaklaşık bir haftadır olan sol ayak sırtında kızarıklık ve şişlik şikayeti ile dermatoloji polikliniğine başvuran hastada selülit tespit edilerek antibiyotik tedavileri başlanmış ve hasta kontrolsüz diyabet açısından endokrinoloji polikliniğine yönlendirilmişti. Endokrinoloji polikliniğinde değerlendirilen hasta kontrolsüz Tip 2 Diabetes Mellitus (DM) sol bacakta selülit, diyabetik periferik nöropati ön tanıları ile endokrinoloji kliniğine yatırıldı. Hastanın öyküsünde yaklaşık 10 yıldır bacaklarda uyuşma, karıncalanma, yanma şikayetleri mevcuttu. 6 yıl önce her iki ayak tabanın delindiğini ve haftalarca süren akıntı olduğunu ifade ediyordu. Son bir haftadır sol ayak sırtında kızarıklık, ısı artışı ve şişlik olduğunu

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Düzelmeyen hastalar için, tedavi algoritmasında bir sonraki adım olarak, farklı ilaç sınıflarından iki ilacın kullanıldığı kombinasyon tedavisi önerilir. Bu ilaçların hiçbirini tolere edemeyen hastalar için alternatif tedaviler, kapsaisin kremi, lidokain yaması, alfa-lipoik asit, izosorbid dinitrat topikal spreyi ve deri altı elektiriksel sinir stimülasyonunu içerir.

**Anahtar Kelimeler:** Diyabet, periferik nöropati

## KAYNAKÇA

1. Ersoy, CÖ. (2015) Diyabet ve sinir sistemi: Periferik nöropati. Şazi İmamoğlu (Ed.),Geçmişten geleceğe diabetes mellitus içinde s.(363-370). Ankara: BAYT Bilimsel araştırmalar basın yayını
2. Vinik AI, Nevoret M-L, Casellini C, Parson HJE, Clinics M. Diabetic neuropathy. 2013;42(4):747-87.
3. Partanen J, Niskanen L, Lehtinen J, Mervaala E, Siitonen O, Uusitupa M. Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. The New England journal of medicine. 1995 Jul 13;333(2):89-94.
4. Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman ELJTIN. Diabetic neuropathy: clinical manifestations and current treatments. 2012;11(6):521-34.
5. Malik RA, Veves A, Walker D, Siddique I, Lye RH, Schady W, et al. Sural nerve fibre pathology in diabetic patients with mild neuropathy: relationship to pain, quantitative sensory testing and peripheral nerve electrophysiology. Acta neuropathologica. 2001 Apr;101(4):367-74.
6. Kles KA, Vinik AI. Pathophysiology and treatment of diabetic peripheral neuropathy: the case for diabetic neurovascular function as an essential component. Current diabetes reviews. 2006 May;2(2):131-45.
7. Malik RA, Tesfaye S, Newrick PG, Walker D, Rajbhandari SM, Siddique I, et al. Sural nerve pathology in diabetic patients with minimal but progressive neuropathy. Diabetologia. 2005 Mar;48(3):578-85.
8. Pftzner A, Forst T, Engelbach M, Margin T, Goitom K, Lobig M, et al. The influence of isolated small nerve fibre dysfunction on microvascular control in patients with diabetes mellitus. Diabetic medicine : a journal of the British Diabetic Association. 2001 Jun;18(6):489-94.
9. Genuth S. Insights from the diabetes control and complications trial/epidemiology of diabetes interventions and complications study on the use of intensive glycemic treatment to reduce the risk of complications of type 1 diabetes. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2006 Jan-Feb;12 Suppl 1:34-41.
10. Dyck PJ, Davies JL, Wilson DM, Service FJ, Melton LJ, 3rd, O'Brien PC. Risk factors for severity of diabetic polyneuropathy: intensive longitudinal assessment of the Rochester Diabetic Neuropathy Study cohort. Diabetes care. 1999 Sep;22(9):1479-86.
11. Jaiswal M, Divers J, Dabelea D, Isom S, Bell RA, Martin CL, et al. Prevalence of and Risk Factors for Diabetic Peripheral Neuropathy in Youth With Type 1 and Type 2 Diabetes: SEARCH for Diabetes in Youth Study. Diabetes care. 2017 Sep;40(9):1226-32.
12. Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL. Diabetic neuropathy: clinical manifestations and current treatments. The Lancet Neurology. 2012 Jun;11(6):521-34.
13. Edwards JL, Vincent AM, Cheng HT, Feldman EL. Diabetic neuropathy: mechanisms to management. Pharmacology & therapeutics. 2008 Oct;120(1):1-34.
14. Feldman EL, Nave KA, Jensen TS, Bennett DLH. New Horizons in Diabetic Neuropathy: Mechanisms, Bioenergetics, and Pain. Neuron. 2017 Mar 22;93(6):1296-313.
15. Thornalley PJ. Glycation in diabetic neuropathy: characteristics, consequences, causes, and therapeutic options. International review of neurobiology. 2002;50:37-57.

16. Sugimoto K, Yasujima M, Yagihashi S. Role of advanced glycation end products in diabetic neuropathy. *Current pharmaceutical design*. 2008;14(10):953-61.
17. Singh R, Barden A, Mori T, Beilin L. Advanced glycation end-products: a review. *Diabetologia*. 2001 Feb;44(2):129-46.
18. Oates PJ. Aldose reductase, still a compelling target for diabetic neuropathy. *Current drug targets*. 2008 Jan;9(1):14-36.
19. Du X, Edelstein D, Brownlee M. Oral benfotiamine plus alpha-lipoic acid normalises complication-causing pathways in type 1 diabetes. *Diabetologia*. 2008 Oct;51(10):1930-2.
20. Das Evcimen N, King GL. The role of protein kinase C activation and the vascular complications of diabetes. *Pharmacological research*. 2007 Jun;55(6):498-510.
21. Pacher P, Obrosova IG, Mabley JG, Szabo C. Role of nitrosative stress and peroxynitrite in the pathogenesis of diabetic complications. Emerging new therapeutical strategies. *Current medicinal chemistry*. 2005;12(3):267-75.
22. Pop-Busui R, Sima A, Stevens M. Diabetic neuropathy and oxidative stress. *Diabetes/metabolism research and reviews*. 2006 Jul-Aug;22(4):257-73.
23. Vincent AM, McLean LL, Backus C, Feldman EL. Short-term hyperglycemia produces oxidative damage and apoptosis in neurons. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*. 2005 Apr;19(6):638-40.
24. Fagerberg SE. Diabetic neuropathy: a clinical and histological study on the significance of vascular affections. *Acta medica Scandinavica Supplementum*. 1959;345:1-97.
25. Dyck PJ, Hansen S, Karnes J, O'Brien P, Yasuda H, Windebank A, et al. Capillary number and percentage closed in human diabetic sural nerve. *Proceedings of the National Academy of Sciences of the United States of America*. 1985 Apr;82(8):2513-7.
26. Dyck PJ, Karnes JL, O'Brien P, Okazaki H, Lais A, Engelstad J. The spatial distribution of fiber loss in diabetic polyneuropathy suggests ischemia. *Annals of neurology*. 1986 May;19(5):440-9.
27. Newrick PG, Wilson AJ, Jakubowski J, Boulton AJ, Ward JD. Sural nerve oxygen tension in diabetes. *British medical journal (Clinical research ed)*. 1986 Oct 25;293(6554):1053-4.
28. Kennedy JM, Zochodne DW. The regenerative deficit of peripheral nerves in experimental diabetes: its extent, timing and possible mechanisms. *Brain : a journal of neurology*. 2000 Oct;123 ( Pt 10):2118-29.
29. Kennedy JM, Zochodne DW. Impaired peripheral nerve regeneration in diabetes mellitus. *Journal of the peripheral nervous system : JPNS*. 2005 Jun;10(2):144-57.
30. Holman RR, Dornan TL, Mayon-White V, Howard-Williams J, Orde-Peckar C, Jenkins L, et al. Prevention of deterioration of renal and sensory-nerve function by more intensive management of insulin-dependent diabetic patients. A two-year randomised prospective study. *Lancet*. 1983 Jan 29;1(8318):204-8.
31. Effect of intensive diabetes treatment on nerve conduction in the Diabetes Control and Complications Trial. *Annals of neurology*. 1995 Dec;38(6):869-80.
32. Perkins BA, Bril V. Early vascular risk factor modification in type 1 diabetes. *The New England journal of medicine*. 2005 Jan 27;352(4):408-9.
33. Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes care*. 2005 Apr;28(4):956-62.
34. Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. 2017;40(1):136-54.
35. Bastron JA, Thomas JE. Diabetic polyradiculopathy: clinical and electromyographic findings in 105 patients. *Mayo Clinic proceedings*. 1981 Dec;56(12):725-32.
36. Chan YC, Lo YL, Chan ES. Immunotherapy for diabetic amyotrophy. *The Cochrane database of systematic reviews*. 2017 Jul 26;7:Cd006521.
37. Brown MR, Dyck PJ, McClearn GE, Sima AA, Powell HC, Porte D, Jr. Central and peripheral nervous system complications. *Diabetes*. 1982;31(Suppl 1 Pt 2):65-70.
38. Dyck PJ, Kratz KM, Karnes JL, Litchy WJ, Klein R, Pach JM, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology*. 1993 Apr;43(4):817-24.

39. Steel JM, Young RJ, Lloyd GG, Clarke BF. Clinically apparent eating disorders in young diabetic women: associations with painful neuropathy and other complications. *British medical journal (Clinical research ed)*. 1987 Apr 4;294(6576):859-62.
40. Tesfaye S, Malik R, Harris N, Jakubowski JJ, Mody C, Rennie IG, et al. Arterio-venous shunting and proliferating new vessels in acute painful neuropathy of rapid glycaemic control (insulin neuritis). *Diabetologia*. 1996 Mar;39(3):329-35.
41. Gibbons CH, Freeman R. Treatment-induced neuropathy of diabetes: an acute, iatrogenic complication of diabetes. *Brain : a journal of neurology*. 2015 Jan;138(Pt 1):43-52.
42. Ellenberg M. Diabetic neuropathic cachexia. *Diabetes*. 1974 May;23(5):418-23.
43. Neal JM. Diabetic neuropathic cachexia: a rare manifestation of diabetic neuropathy. *Southern medical journal*. 2009 Mar;102(3):327-9.
44. Callaghan BC, Price RS, Feldman EL. Distal Symmetric Polyneuropathy: A Review. *Jama*. 2015 Nov 24;314(20):2172-81.
45. Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, et al. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes care*. 2017 Jan;40(1):136-54.
46. Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N, Greene DA. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. *Diabetes care*. 1994 Nov;17(11):1281-9.
47. Griebeler ML, Morey-Vargas OL, Brito JP, Tsapas A, Wang Z, Carranza Leon BG, et al. Pharmacologic interventions for painful diabetic neuropathy: An umbrella systematic review and comparative effectiveness network meta-analysis. *Annals of internal medicine*. 2014 Nov 4;161(9):639-49.
48. Ruhnau KJ, Meissner HP, Finn JR, Reljanovic M, Lobisch M, Schutte K, et al. Effects of 3-week oral treatment with the antioxidant thioctic acid (alpha-lipoic acid) in symptomatic diabetic polyneuropathy. *Diabetic medicine : a journal of the British Diabetic Association*. 1999 Dec;16(12):1040-3.
49. Ametov AS, Barinov A, Dyck PJ, Hermann R, Kozlova N, Litchy WJ, et al. The sensory symptoms of diabetic polyneuropathy are improved with alpha-lipoic acid: the SYDNEY trial. *Diabetes care*. 2003 Mar;26(3):770-6.
50. Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. 2011;3(4):345-52. e21.
51. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Annals of internal medicine*. 2010 Jan 19;152(2):85-92.
52. Dubinsky RM, Miyasaki J. Assessment: efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2010 Jan 12;74(2):173-6.
53. Sima AA, Calvani M, Mehra M, Amato A. Acetyl-L-carnitine improves pain, nerve regeneration, and vibratory perception in patients with chronic diabetic neuropathy: an analysis of two randomized placebo-controlled trials. *Diabetes care*. 2005 Jan;28(1):89-94.
54. Yuen KC, Baker NR, Rayman G. Treatment of chronic painful diabetic neuropathy with isosorbide dinitrate spray: a double-blind placebo-controlled cross-over study. *Diabetes care*. 2002 Oct;25(10):1699-703.
55. Cohen KL, Harris S. Efficacy and safety of nonsteroidal anti-inflammatory drugs in the therapy of diabetic neuropathy. *Archives of internal medicine*. 1987 Aug;147(8):1442-4.
56. Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology,

the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2011 May 17;76(20):1758-65.

57. de Vos CC, Meier K, Zaalberg PB, Nijhuis HJ, Duyvendak W, Vesper J, et al. Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. *Pain*. 2014 Nov;155(11):2426-31.
58. Boulton AJ, Malik RA, Arezzo JC, Sosenko JM. Diabetic somatic neuropathies. *Diabetes care*. 2004 Jun;27(6):1458-86.