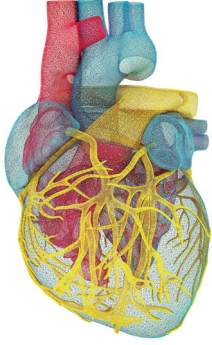


# BÖLÜM 31



## Kardiyovasküler Hastalıklar ve Hipertansiyon Tedavisinde Kullanılan Ajanların Glukoz Metabolizması Üzerine Etkileri

Muhammed Fuad USLU<sup>1</sup>

### | GİRİŞ

Kronik hastalıklar içerisinde kardiyovasküler hastalıklar (KVH) önemli bir yere sahip olmakla beraber ülkemizde ve Dünyada en önemli ölüm nedenleri arasında yer almaktadır (1,2).

Her geçen gün artan mortalite ve morbiditesi göz önüne alındığında kardiyovasküler hastalıklarda kullanılan tedavi ajanlarının etkilerini yakından takip etmenin önemi açıktır. Bu bölümde Kardiyovasküler hastalıklar ve hipertansiyon tedavisinde kullanılan ajanların glukoz metabolizması üzerine etkileri ele alınmış ve işlenmiştir.

### Kardiyovasküler Hastalıklar ve Hipertansiyon Tedavisinde Kullanılan Ajanların Glukoz Metabolizması Üzerine Etkileri

Anjiotensin dönüştürücü enzim (ACE) inhibitörleri ile yapılmış bazı çalışmalarda bu grup ilaçlar diyabetli hipertansiyon hastalarında diyabetin ilerlemesini geciktirmekte ya da önlemektedirler. Bunu da mikrodolaşımı ve kan şekeri regülasyonunu iyileştirerek, insülin sensitivitesini ve glukoz kullanımını arttırarak sağlamaktadır (3).

Öte yandan, bazı çalışmalar ACE inhibitörlerinin metabolizması üzerinde nötr bir etkiye sahip olduğunu göstermiştir. T2DM ve hipertansiyonu olan hastalarda ( $n = 24$ ) yapılan bir çalışma, trandolapril tedavisinden sonra insülin duyarlılığında hiçbir değişiklikle sonuçlanmadığı belirtilmiştir (4). Lisinopril tedavisi, klortalidon ile tedavi edilen hastalara kıyasla T2DM geliştirme riskini %30, amlodipin ile %17 kadar azaltmıştır (5).

Sol ventrikül disfonksiyonu (SOLVD) çalışmaları, asemptomatik sol ventrikül (LV) disfonksiyonu olan hastaları ortalama 37,4 aylık takip için enalapril veya plasebo alacak şekilde randomize eden çift kör bir çalışmadır. Enalapril, plaseboya kıyasla kalp yetmezliği insidansını ve ilgili hastaneye yatış oranını önemli ölçüde azaltmıştır. Geriye dönük bir çalışma, SOLVD çalışmasındaki hastalarda enalapril'in diyabet insidansı üzerindeki etkisini değerlendirmiş olup, Enalaprilin plaseboya kıyasla diyabet insidansını önemli ölçüde azalttığı gözlenmiştir (6,7).

DREAM çalışması, hastalarda ramipril veya plasebonun etkilerini değerlendirmiş olup ( $n=5.269$ ), KVH olmayan ancak bozulmuş açlık glu-

<sup>1</sup> Uzm. Dr., Fethi Sekin Şehir Hastanesi, İç Hastalıkları, dr.fuslu@gmail.com

olay riskinde sağlanan yarar çok daha fazla olduğundan statin kullanmaktan kaçınmamak gerekir.

## KAYNAKLAR

1. Türkiye İstatistik Kurumu. *Ölüm Nedeni İstatistikleri 2018*.
2. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation* 2017;135(10):e146–e603. doi: 10.1161/CIR.0000000000000485.
3. Diyabetes mellituslu hastaların tedavisinde hipoglisemi. *Türkiye Klinikleri Endocrinology - Special Topics*, 1(1), 92-100.
4. New JP, Bilous RW, Walker M. Insulin sensitivity in hypertensive Type 2 diabetic patients after 1 and 19 days' treatment with trandolapril. *Diabetic medicine*. 2000;17:134–140. doi: 10.1046/j.1464-5491.2000.00235.x
5. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) *JAMA*. 2002;288:2981–2997. doi: 10.1001/jama.288.23.2981.
6. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *The New England journal of medicine*. 1992;327:685–691. doi:10.1056/NEJM199209033271003.
7. 30. Vermees E, Ducharme A, Bourassa MG, et al. Enalapril reduces the incidence of diabetes in patients with chronic heart failure: insight from the Studies Of Left Ventricular Dysfunction (SOLVD) *Circulation*. 2003;107:1291–1296. doi: 10.1161/01.cir.0000054611.89228.92.
8. DREAM Trial Investigators, Bosch J, Yusuf S, Gerstein HC. Effect of ramipril on the incidence of diabetes. *The New England journal of medicine*. 2006;355:1551–1562. doi: 10.1056/NEJMoa065061
9. DREAM On Investigators, Gerstein HC, Mohan V, Avezum A, et al. Long-term effect of rosiglitazone and/or ramipril on the incidence of diabetes. *Diabetologia*. 2011;54:487–495. doi: 10.1007/s00125-010-1985-4.
10. Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995–1003. doi: 10.1016/S0140-6736(02)08089-3.
11. Lindholm LH, Persson M, Alaupovic P, et al. Metabolic outcome during 1 year in newly detected hypertensives: results of the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE study). *Journal of Hypertension*. 2003;21:1563–1574. doi: 10.1097/01.hjh.0000084723.53355.76.
12. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363:2022–2031. doi: 10.1016/S0140-6736(04)16451-9.
13. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet*. 2003;362:759–766. doi: 10.1016/s0140-6736(03)14282-1.
14. Benson SC, Pershadsingh HA, Ho CI, et al. Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPAR gamma-modulating activity. *Hypertension*. 2004;43:993–1002. doi: 10.1161/01.HYP.0000123072.34629.57.
15. Schupp M, Janke J, Clasen R, et al. Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor-gamma activity. *Circulation*. 2004;109:2054–2057. doi: 10.1161/01.CIR.0000127955.36250.65.
16. De Rosa ML, Musella F, Ilardi F, et al. Effects of antihypertensive therapy on glucose, insulin metabolism, left ventricular diastolic dysfunction and renin system in overweight and obese hypertensives. *Journal of the renin-angiotensin-aldosterone system*. 2013;15:196–204. doi: 10.1177/1470320312474053.
17. Noto H, Goto A, Tsujimoto T, et al. Effect of calcium channel blockers on incidence of diabetes: a meta-analysis. *Diabetes, metabolic syndrome and obesity*. 2013;6:257–261. doi: 10.2147/DMSO.S49767.
18. Yang Y, Wei RB, Xing Y, et al. A meta-analysis of the effect of angiotensin receptor blockers and calcium channel blockers on blood pressure, glycemia and the HOMA-IR index in non-diabetic patients. *Metabolism: Clinical and Experimental*. 2013;62:1858–1866. doi: 10.1016/j.metabol.2013.08.008.
19. Levine M, Boyer EW, Pozner CN, et al. Assessment of hyperglycemia after calcium channel blocker overdoses involving diltiazem or verapamil. *Critical Care Medicine*. 2007;35:2071–2075. doi: 10.1097/01.ccm.0000278916.04569.23.
20. Pollare T, Lithell H, Mörlin C, et al. Metabolic effects of diltiazem and atenolol: results from a randomized, double-blind study with parallel groups. *Journal of Hypertension*. 1989;7:551–559. doi: 10.1097/00004872-198907000-00006.
21. Lithell H, Pollare T, Vessby B. Metabolic effects of pindolol and propranolol in a double-blind crossover study in hypertensive patients. *Blood Pressure*. 1992;1:92–101. doi: 10.3109/08037059209077499.
22. Taylor EN, Hu FB, Curhan GC. Antihypertensive medications and the risk of incident type 2 diabetes. *Diabetes Care*. 2006;29:1065–1070. doi: 10.2337/diacare.2951065.
23. Gress TW, Nieto FJ, Shahar E, et al. Hypertension and antihypertensive therapy as risk factors

- for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *The New England journal of medicine*. 2000;342:905–912. doi:10.1056/NEJM200003303421301.
24. Shen L, Shah BR, Reyes EM, et al. Role of diuretics,  $\beta$  blockers, and statins in increasing the risk of diabetes in patients with impaired glucose tolerance: reanalysis of data from the NAVIGATOR study. *BMJ*. 2013;347:f6745. doi: 10.1136/bmj.f6745.
  25. Lithell H, Pollare T, Berne C, et al. The metabolic and circulatory response to beta-blockade in hypertensive men is correlated to muscle capillary density. *Blood Pressure*. 1992;1:20–26. doi: 10.3109/08037059209065120.
  26. Lund-Johansen P, Omvik P, Nordrehaug JE. Long-term hemodynamic effects of antihypertensive treatment. *The Clinical investigator*. 1992;70 Suppl 1:S58–S64. doi: 10.1007/BF00207613.
  27. Rössner S, Taylor CL, Byington RP, et al. Long term propranolol treatment and changes in body weight after myocardial infarction. *BMJ*. 1990;300:902–903. doi: 10.1136/bmj.300.6729.902.
  28. Ye J. Mechanisms of insulin resistance in obesity. *Frontiers of medicine*. 2013;7:14–24. doi: 10.1007/s11684-013-0262-6
  29. Lindholm LH, Persson M, Alaupovic P, et al. Metabolic outcome during 1 year in newly detected hypertensives: results of the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE study). *Journal of Hypertension*. 2003;21:1563–1574. doi: 10.1097/01.hjh.0000084723.53355.76.1A-garwal R. Hypertension, hypokalemia, and thiazide-induced diabetes: a 3-way connection. *Hypertension*. 2008;52:1012–1013. doi: 10.1161/HYPERTENSIONAHA.108.121970
  30. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet*. 2007;369:201–207. doi: 10.1016/S0140-6736(07)60108-1.
  31. Barzilay JI, Davis BR, Cutler JA, et al. Fasting glucose levels and incident diabetes mellitus in older nondiabetic adults randomized to receive 3 different classes of antihypertensive treatment: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Archives of internal medicine*. 2006;166:2191–2201. doi: 10.1001/archinte.166.20.2191.
  32. Verdecchia P, Reboldi G, Angeli F, et al. Adverse prognostic significance of new diabetes in treated hypertensive subjects. *Hypertension*. 2004;43:963–969. doi: 10.1161/01.HYP.0000125726.92964.ab.
  33. Cutler JA. Thiazide-associated glucose abnormalities: prognosis, etiology, and prevention: is potassium balance the key? *Hypertension*. 2006;48:198–200. doi: 10.1161/01.HYP.0000231339.51310.b3.
  34. Zillich AJ, Garg J, Basu S, et al. Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension*. 2006;48:219–224. doi: 10.1161/01.HYP.0000231552.10054.aa.
  35. Kao WH, Folsom AR, Nieto FJ, et al. Serum and dietary magnesium and the risk for type 2 diabetes mellitus: the Atherosclerosis Risk in Communities Study. *Archives of internal medicine*. 1999;159:2151–2159. doi: 10.1001/archinte.159.18.2151.
  36. Van Dam RM, Hu FB, Rosenberg L, et al. Dietary calcium and magnesium, major food sources, and risk of type 2 diabetes in U.S. black women. *Diabetes Care*. 2006;29:2238–2243. doi: 10.2337/dc06-1014.
  37. Eriksson JW, Jansson PA, Carlberg B, et al. Hydrochlorothiazide, but not Candesartan, aggravates insulin resistance and causes visceral and hepatic fat accumulation: the mechanisms for the diabetes preventing effect of Candesartan (MEDICA) Study. *Hypertension*. 2008;52:1030–1037. doi: 10.1161/HYPERTENSIONAHA.108.119404.
  38. Kurihara Y, Douzono T, Kawakita K, et al. A largescale, long-term, prospective post-marketing surveillance of pitavastatin (LIVALO\_ Tablet)-LIVALO Effectiveness and safety (LIVES) Study. *Japanese Pharmacology & Therapeutics* 2008;36:709–31. doi: 10.5551/jat.3764.
  39. Gumprecht J, Goshu M, Budinski D, et al. Comparative long-term efficacy and tolerability of pitavastatin 4 mg and atorvastatin 20–40 mg in patients with type 2 diabetes mellitus and combined (mixed) dyslipidaemia. *Diabetes. Obes. Metab* 2011;13:1047–55. doi: 10.1111/j.1463-1326.2011.01477.x.
  40. Ray K. Statin diabetogenicity: Guidance for clinicians. *Cardiovascular Diabetology* 2013; 12 (Suppl 1): 3. doi: 10.1186/1475-2840-12-S1-S3.
  41. Ma Y, Culver A, Rossouw J, et al. Statin therapy and the risk for diabetes among adult women: do the benefits outweigh the risk? *The Adv Cardiovasc Dis* 2013; 7(1): 41-4. doi: 10.1177/1753944712468499.
  42. American Diabetes Association. Standards of medical care in diabetes-2014. *Diabetes Care* 2014; 37(Suppl 1): 14-80. doi: 10.2337/dc14-S014.
  43. Rocco MB. Statins and diabetes risk: fact, fiction, and clinical implications. *Cleveland Clinic journal of medicine* 2012; 79 (12): 883-93. doi: 10.3949/ccjm.79a.12091.
  44. Freeman DJ, Norrie J, Sattar N, et al. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation* 2001, 103: 357-62. doi: 10.1161/01.cir.103.3.357.