



4. Bölüm

COVID-19 ve Diyabet

Hakan DOĞRUEL¹

GENEL BİLGİLER

Coronavirüsler, insanlarda ve hayvanlarda enfeksiyona neden olabilen önemli patojenlerdir. İlk olarak Çin Halk Cumhuriyeti'nin Wuhan kentinde, 2019 yılı sonlarında tanımlanan ve akut respiratuvar sendrom coronavirus-2'nin (SARS-CoV-2) neden olduğu COVID-19 kısa sürede bütün dünyaya yayıldı. Dünya sağlık örgütü (DSÖ) tarafından Mart 2020'de pandemi olarak ilan edildi (1). COVID-19 pandemisi, kısa sürede son yüzyılın en önemli sağlık sorunlarından biri haline geldi.

DSÖ tarafından pandemi olarak ilan edilmiş diğer bir hastalık Diyabetes Mellitus (DM) ise, hiperglisemi ile karakterize sürekli tıbbi bakım gerektiren bir kronik metabolik hastalıktır (2). Son yıllarda DM sıklığı giderek artmaktadır. Tüm dünyada DM vaka sayısının; 2009' da 285 milyon, 2011' de 366 milyon, 2015' te 415 milyon, 2017' de ise 425 milyon olduğu tahmin edilmektedir. Ayrıca tüm dünya genelinde 2030'da 578 milyon, 2045' te ise 700 milyon DM tanılı bireyin olacağı tahmin edilmektedir (3). DM varlığı birçok hastalık durumunda klinik sonuçları olumsuz etkilemektedir. DM hastalarında, DM olmayan hastalara göre akut koroner sendrom (AKS) sonrası klinik sonuçların daha kötü olduğu birçok çalışmada gösterilmiştir (4-7). Ayrıca herhangi bir sebeple cerrahi girişim yapılan hastalarda, DM varlığının daha sık komplikasyon ile ilişkili olduğu saptanmıştır (8-12). DM tanılı hastaların, DM olmayanlara göre enfeksiyonlara daha yatkın olduğu da birçok çalışmada gösterilmiştir (13-15). Nötrofil kemotaksisi, nötrofilin

¹ Uzm. Dr., Akdeniz Üniversitesi Tıp Fakültesi Endokrinoloji ve Metabolizma Hastalıkları BD, dogruelhakan@gmail.com

Sonuç olarak; COVID-19 ve DM birbirlerinin klinik seyrini etkileyen önemli sağlık sorunlarıdır. COVID-19 enfeksiyonu varlığında DM'nin klinik gidişatı olumsuz etkilemesinin yanında COVID-19 enfeksiyonun glisemik bozukluk ve yeni DM gelişimine yol açabileceği akılda tutulmalıdır. Hiperglisemi yönetiminde bireyleri hipoglisemi, hiperglisemi ve glisemik dalgalanmalardan korumanın yanında anti-diyabetik ajanların spesifik kontrendikasyonları ve dikkat edilmesi gereken hususlar göz ardı edilmemelidir.

KAYNAKLAR

1. World Health O. Coronavirus disease 2019 (COVID-19): situation report, 114. Geneva: World Health Organization; 2020 2020-05-13.
2. Dogruel H, Balci MK. Development of therapeutic options on type 2 diabetes in years: Glucagon-like peptide-1 receptor agonist's role intreatment; from the past to future. World journal of diabetes. 2019;10(8):446. doi: 10.4239/wjd.v10.i8.446
3. 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 research and clinical practice. 2019;157:107843. doi: 10.1016/j.diabetes.2019.107843
4. Donahoe SM, Stewart GC, McCabe CH, et al. Diabetes and mortality following acute coronary syndromes. Jama. 2007;298(7):765-75. doi: 10.1001/jama.298.7.765
5. Granger CB, Califf RM, Young S, et al. Outcome of patients with diabetes mellitus and acute myocardial infarction treated with thrombolytic agents. Journal of the American College of Cardiology. 1993;21(4):920-5. doi: 10.1016/0735-1097(93)90348-5
6. Savage MP, Krolewski AS, Kenien GG, et al. Acute myocardial infarction in diabetes mellitus and significance of congestive heart failure as a prognostic factor. The American journal of cardiology. 1988;62(10):665-9. doi: 10.1016/0002-9149(88)91199-x
7. Stone PH, Muller JE, Hartwell T, et al. The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of both coronary disease and diastolic left ventricular dysfunction to the adverse prognosis. Journal of the American College of Cardiology. 1989;14(1):49-57. doi: 10.1016/0735-1097(89)90053-3
8. Belmont Jr PJ, Davey S, Rensing N, et al. Patient-based and surgical risk factors for 30-day postoperative complications and mortality after ankle fracture fixation. Journal of orthopaedic trauma. 2015;29(12):e476-e82. doi: 10.1097/BOT.0000000000000328
9. Chuah LL, Papamargaritis D, Pillai D, et al. Morbidity and mortality of diabetes with surgery. Nutricion hospitalaria. 2013;28(2):47-52. doi: 10.3305/nh.2013.28.sup2.6713
10. Corrigan KE, Vargas MV, Robinson HN, et al. Impact of diabetes mellitus on postoperative complications following laparoscopic hysterectomy for benign indications. Gynecologic and obstetric investigation. 2019;84(6):583-90. Doi: 10.1159/000501034
11. Rollins KE, Varadhan KK, Dhataria K, et al. Systematic review of the impact of HbA1c on outcomes following surgery in patients with diabetes mellitus. Clinical Nutrition. 2016;35(2):308-16. doi: 10.1016/j.clnu.2015.03.007
12. Rosado P, Cheng HT, Wu CM, et al. Influence of diabetes mellitus on postoperative complications and failure in head and neck free flap reconstruction: A systematic review and meta-analysis. Head & neck. 2015;37(4):615-8. doi: 10.1002/hed.23624
13. Abu-Ashour W, Twells LK, Valcour JE, et al. Diabetes and the occurrence of infection in primary care: a matched cohort study. BMC infectious diseases. 2018;18(1):1-8. doi: 10.1186/s12879-018-2975-2

14. Carey IM, Critchley JA, DeWilde S, et al. Risk of infection in type 1 and type 2 diabetes compared with the general population: a matched cohort study. *Diabetes care*. 2018;41(3):513-21. doi: 10.2337/dc17-2131
15. Mor A, Berencsi K, Nielsen JS, et al. Rates of community-based antibiotic prescriptions and hospital-treated infections in individuals with and without type 2 diabetes: a Danish nationwide cohort study, 2004–2012. *Reviews of Infectious Diseases*. 2016;63(4):501-11. doi: 10.1093/cid.ciw345
16. Delamaire M, Maugeudre D, Moreno M, et al. Impaired leucocyte functions in diabetic patients. *Diabetic Medicine*. 1997;14(1):29-34. doi: 10.1002/(SICI)1096-9136(199701)14:1<29::AID-DIA300>3.0.CO;2-V
17. Hostetter MK. Handicaps to host defense: effects of hyperglycemia on C3 and *Candida albicans*. *Diabetes*. 1990;39(3):271-5. doi: 10.2337/diab.39.3.271
18. Llorente L, De La Fuente H, Richaud-Patin Y, et al. Innate immune response mechanisms in non-insulin dependent diabetes mellitus patients assessed by flow cytometry. *Immunology letters*. 2000;74(3):239-44. doi: 10.1016/s0165-2478(00)00255-8
19. Comino EJ, Harris MF, Islam MF, et al. Impact of diabetes on hospital admission and length of stay among a general population aged 45 year or more: a record linkage study. *BMC health services research*. 2015;15(1):1-13. doi: 10.1186/s12913-014-0666-2
20. Barron E, Bakhai C, Kar P, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *The lancet Diabetes & endocrinology*. 2020;8(10):813-22. doi: 10.1016/S2213-8587(20)30272-2
21. De Almeida-Pititto B, Dualib PM, Zajdenverg L, et al. Severity and mortality of COVID-19 in patients with diabetes, hypertension and cardiovascular disease: a meta-analysis. *Diabetology & metabolic syndrome*. 2020;12(1):1-12. doi: 10.1186/s13098-020-00586-4
22. Liu S-p, Zhang Q, Wang W, et al. Hyperglycemia is a strong predictor of poor prognosis in COVID-19. *Diabetes research and clinical practice*. 2020;167:108338. doi: 10.1016/j.diabres.2020.108338
23. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *Jama*. 2020;323(13):1239-42. doi: 10.1001/jama.2020.2648
24. Barone MTU, Ngongo B, Harnik SB, et al. COVID-19 associated with diabetes and other non-communicable diseases led to a global health crisis. *Diabetes research and clinical practice*. 2021;171:108587. doi: 10.1016/j.diabres.2020.108587
25. Wexler DJ. COVID-19: Issues related to diabetes mellitus in adults. 2020. https://www.up-to-date.com/contents/COVID-19-issues-related-to-diabetes-mellitus-in-adults?search=Wexler%20DJ.%20COVID-19:%20Issues%20related%20to%20diabetes%20mellitus%20in%20adults.%202020.&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
26. Zhu L, She Z-G, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. *Cell metabolism*. 2020;31(6):1068-77. e3. doi: 10.1016/j.cmet.2020.04.021
27. Apicella M, Campopiano MC, Mantuano M, et al. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. *The lancet Diabetes & endocrinology*. 2020. doi: 10.1016/S2213-8587(20)30238-2
28. Cariou B, Hadjadj S, Wargny M, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia*. 2020;63(8):1500-15. doi: 10.1007/s00125-020-05180-x
29. Jafar N, Edriss H, Nugent K. The effect of short-term hyperglycemia on the innate immune system. *The American journal of the medical sciences*. 2016;351(2):201-11. doi: 10.1016/j.amjms.2015.11.011

30. Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes/metabolism research and reviews*. 2020;36(7):e3319. doi: 10.1002/dmrr.3319
31. Pal R, Bhadada SK. COVID-19 and diabetes mellitus: An unholy interaction of two pandemics. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2020;14(4):513-7. doi: 10.1016/j.dsx.2020.04.049
32. Dunn E, Grant P. Type 2 diabetes: an atherothrombotic syndrome. *Current Molecular Medicine*. 2005;5(3):323-32. doi: 10.2174/1566524053766059
33. Hussain A, Bhowmik B, do Vale Moreira NC. COVID-19 and diabetes: Knowledge in progress. *Diabetes research and clinical practice*. 2020;108142. doi: 10.1016/j.diabres.2020.108142
34. Kutlutürk F. COVID-19 Pandemisi ve Diabetes Mellitus. *Türkiye Diyabet ve Obezite Dergisi*. 2020;4(2):130-7. doi: 10.25048/tudod.746139
35. Pal R, Bhansali A. COVID-19, diabetes mellitus and ACE2: the conundrum. *Diabetes research and clinical practice*. 2020;162. doi: 10.1016/j.diabres.2020.108132
36. Chen J, Wu C, Wang X, et al. The impact of COVID-19 on blood glucose: A systematic review and meta-analysis. *Frontiers in endocrinology*. 2020;11. doi: 10.3389/fendo.2020.574541
37. Sönmezer MÇ., İnkaya AÇ. COVID-19: Viroloji, Patogenez, Klinik Özellikler ve Tedavi. 1. Baskı. Ankara: Türkiye Klinikleri; 2020. p.1-8
38. Lim S, Bae JH, Kwon H-S, et al. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nature Reviews Endocrinology*. 2020;1-20. doi: 10.1038/s41574-020-00435-4
39. Yang J-K, Lin S-S, Ji X-J, et al. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta diabetologica*. 2010;47(3):193-9. doi: 10.1007/s00592-009-0109-4
40. Wu L, Girgis CM, Cheung NW. COVID-19 and diabetes: Insulin requirements parallel illness severity in critically unwell patients. *Clinical Endocrinology*. 2020;93(4):390-3. doi: 10.1111/cen.14288
41. Ren H, Yang Y, Wang F, et al. Association of the insulin resistance marker TyG index with the severity and mortality of COVID-19. *Cardiovascular diabetology*. 2020;19:1-8. doi: 10.1186/s12933-020-01035-2
42. Reiterer M, Rajan M, Gomez-Banoy N, et al. Hyperglycemia in Acute COVID-19 is Characterized by Adipose Tissue Dysfunction and Insulin Resistance. *medRxiv*. 2021. doi: 10.1101/2021.03.21.21254072
43. Suh S, Park MK. Glucocorticoid-induced diabetes mellitus: an important but overlooked problem. *Endocrinology and metabolism*. 2017;32(2):180. doi: 10.3803/EnM.2017.32.2.180
44. Van Raalte D, Ouwens D, Diamant M. Novel insights into glucocorticoid-mediated diabetogenic effects: towards expansion of therapeutic options? *European journal of clinical investigation*. 2009;39(2):81-93. doi: 10.1111/j.1365-2362.2008.02067.x
45. Horby P, Lim WS, Emberson J, et al. RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19-preliminary report *N Engl J Med*. 2020;1-11. doi: 10.1056/NEJMoa2021436
46. American Diabetes Association. 15. Diabetes Care in the Hospital: Standards of Medical Care in Diabetes—2021. *Diabetes Care*. 2021;44(Supplement 1):S211-S20. doi: 10.2337/dc21-S015
47. Bonikowska K, Magnusson P, Sjöholm A. Life-threatening ketoacidosis in patients with type 2 diabetes on LCHF diet. *Lakartidningen*. 2018;115.
48. Brown F, McColl T. Euglycemic diabetic ketoacidosis secondary to dapagliflozin use: a case report. *The Journal of emergency medicine*. 2018;54(1):109-11. doi: 10.1016/j.jemermed.2017.10.001
49. Qiu H, Novikov A, Vallon V. Ketosis and diabetic ketoacidosis in response to SGLT2 inhibitors: basic mechanisms and therapeutic perspectives. *Diabetes/metabolism research and reviews*. 2017;33(5):e2886. doi: 10.1002/dmrr.2886

50. Storgaard H, Bagger JI, Knop FK, et al. Diabetic ketoacidosis in a patient with type 2 diabetes after initiation of sodium–glucose cotransporter 2 inhibitor treatment. *Basic & clinical pharmacology & toxicology*. 2016;118(2):168-70. doi: 10.1111/bcpt.12457
51. Taylor SI, Blau JE, Rother KI. SGLT2 inhibitors may predispose to ketoacidosis. *The Journal of Clinical Endocrinology & Metabolism*. 2015;100(8):2849-52. doi: 10.1210/jc.2015-1884
52. Chee YJ, Ng SJH, Yeoh E. Diabetic ketoacidosis precipitated by COVID-19 in a patient with newly diagnosed diabetes mellitus. *Diabetes research and clinical practice*. 2020. doi: 10.1016/j.diabres.2020.108166
53. Meza JL, Triana A, De Avila I, et al. Diabetic Ketoacidosis Precipitated by COVID-19 in Patients Without Respiratory Symptoms. *Cureus*. 2020;12(8). doi: 10.7759/cureus.10031
54. Pal R, Banerjee M, Yadav U, et al. Clinical profile and outcomes in COVID-19 patients with diabetic ketoacidosis: a systematic review of literature. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2020;14(6):1563-9. doi: 10.1016/j.dsx.2020.08.015
55. Palermo NE, Sadhu AR, McDonnell ME. Diabetic ketoacidosis in COVID-19: unique concerns and considerations. *The Journal of Clinical Endocrinology & Metabolism*. 2020;105(8):2819-29. doi: 10.1210/clinem/dgaa360
56. Yılmaz M, Kaya A, Balci MK, et al. COVID-19 Pandemi Diyabet İzlem ve Tedavi Kriterleri Uzlaş Raporu. 2020.
57. Noh Y, Oh I-S, Jeong HE, et al. Association Between DPP-4 Inhibitors and COVID-19-Related Outcomes Among Patients With Type 2 Diabetes. *Diabetes care*. 2021;44(4):e64-e6. doi: 0.2337/dc20-1824
58. Wang J, Cooper JM, Gokhale K, et al. Association of metformin with susceptibility to COVID-19 in people with Type 2 diabetes. *The Journal of Clinical Endocrinology & Metabolism*. 2021;106(5):1255-68. doi: 10.1210/clinem/dgab067
59. Lalau J-D, Al-Salameh A, Hadjadj S, et al. Metformin use is associated with a reduced risk of mortality in patients with diabetes hospitalised for COVID-19. *Diabetes & Metabolism*. 2021;47(5):101216. doi: 10.1016/j.diabet.2020.101216
60. Scheen AJ. Metformin and COVID-19: From cellular mechanisms to reduced mortality. *Diabetes & metabolism*. 2020;46(6):423-6. doi: 10.1016/j.diabet.2020.07.006
61. Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. *The lancet Diabetes & endocrinology*. 2020. doi: 10.1016/S2213-8587(20)30152-2
62. American Diabetes Association. Introduction: Standards of Medical Care in Diabetes—2021. *diabetes Care*. 2021 jan;44 (Supply 1): S1-S2. doi: 10.2337/dc21-Sint
63. Carboni E, Carta AR, Carboni E. Can pioglitazone be potentially useful therapeutically in treating patients with COVID-19? Medical hypotheses. 2020;140:109776. doi: 10.1016/j.mehy.2020.109776
64. Raj VS, Mou H, Smits SL, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nature*. 2013;495(7440):251-4. doi: 10.1038/nature12005
65. Reinhold D, Biton A, Goihl A, et al. Dual inhibition of dipeptidyl peptidase IV and aminopeptidase N suppresses inflammatory immune responses. *Annals of the New York Academy of Sciences*. 2007;1110(1):402-9. doi: 10.1196/annals.1423.042
66. Solerte SB, Di Sabatino A, Galli M, et al. Dipeptidyl peptidase-4 (DPP4) inhibition in COVID-19. *Acta diabetologica*. 2020;57:779-83. doi: 10.1007/s00592-020-01539-z
67. Bassendine MF, Bridge SH, McCaughan GW, et al. COVID-19 and comorbidities: A role for dipeptidyl peptidase 4 (DPP4) in disease severity? *Journal of diabetes*. 2020;12(9):649-58. doi: 10.1111/1753-0407.13052
68. Mirani M, Favacchio G, Carrone F, et al. Impact of comorbidities and glycemia at admission and dipeptidyl peptidase 4 inhibitors in patients with type 2 diabetes with COVID-19: a case series from an academic hospital in Lombardy, Italy. *Diabetes care*. 2020;43(12):3042-9. doi: 10.2337/dc20-1340

69. Solerte SB, D'Addio F, Trevisan R, et al. Sitagliptin treatment at the time of hospitalization was associated with reduced mortality in patients with type 2 diabetes and COVID-19: a multicenter, case-control, retrospective, observational study. *Diabetes Care*. 2020;43(12):2999-3006. doi: 10.2337/dc20-1521
70. Roussel R, Darmon P, Pichelin M, et al. Use of dipeptidyl peptidase-4 inhibitors and prognosis of COVID-19 in hospitalized patients with type 2 diabetes: A propensity score analysis from the CORONADO study. *Diabetes, Obesity and Metabolism*. 2021;23(5):1162-72. doi: 10.1111/dom.14324
71. Zhou J-H, Wu B, Wang W-X, et al. No significant association between dipeptidyl peptidase-4 inhibitors and adverse outcomes of COVID-19. *World journal of clinical cases*. 2020;8(22):5576. doi: 10.12998/wjcc.v8.i22.5576
72. Wallace MD, Metzger NL. Optimizing the treatment of steroid-induced hyperglycemia. *Annals of Pharmacotherapy*. 2018;52(1):86-90. doi: 10.1177/1060028017728297
73. Radhakutty A, Burt MG. Management of endocrine disease: critical review of the evidence underlying management of glucocorticoid-induced hyperglycaemia. *European journal of endocrinology*. 2018;179(4):R207-R18. doi: 10.1530/EJE-18-0315
74. Myers AK, Khan M, Choi S, et al. Implementation of a Weight-Based Protocol for the Management of Steroid-Induced Hyperglycemia. *American Journal of Therapeutics*. 2020;27(4):e392-e9. doi: 10.1097/MJT0000000000000998