BÖLÜM 3

DİYABETİK KETOASİDOZ

Eray ÇELİKTÜRK[1]
Ömer SALT[2]

GİRİŞ

Diyabetik Ketoasidoz (DKA), hiperglisemi, yüksek anyon gapli metabolik asidoz, volüm kaybı ve keton birikimi ile karakterize hayatı tehdit edici tıbbi bir acil durumdur (1-3). DKA çoğunlukla tip 1 diyabetin komplikasyonu olarak görülse de, Tip 2 diyabet hastalarında da ketoza eğilimi artıran enfeksiyon, travma, kardiyovasküler vb. durumlarda komplikasyon olarak sıklıkla karşılaşılabilmektedir (4, 5). Çocuklar da dahil olmak üzere birçok kişi DKA ile başvuru sonucunda diyabet tanısı almaktadır (6). Komplikasyonları ve mortaliteyi en aza indirmek için DKA'nın zamanında tanınması oldukça önemlidir (1, 4). DKA, diyabetli hastalarda tanısal testlerin, ilaçların keşfedilip geliştirilmesine rağmen, morbidite ve mortalitenin önde gelen nedenlerinden olmaya devam etmektedir (2, 3, 7).

EPİDEMİYOLOJİ

DKA, genç hastalarda (18-44 yaş) daha sık görülürken, bu hastalar düşük mortaliteye sahiptir. Buna karşın komorbiditesi fazla olan yaşlı hastalar ise daha düşük hastaneye yatış eğilimine, fakat daha yüksek mortaliteye sahiptir (8). DKA'lı hastaların hastaneye yatış oranı(% 1,1), yaşa göre 2000-2009 yılları arasında bir düşüş eğilimi göstermiştir (9). Ancak, 2009-2014 yılları arasında düşüş eğilimi tersine dönerek yaşa göre % 6,3 oranında bir artışı göstermesine rağmen bu süre zarfında hastane içi vaka ölüm oranları, yüzde 1,1'den yüzde 0,4'e düşmüştür (9). Amerika'da DKA insidansı yılda, 18 yaşından büyük hastalarda 1000 kişide 44,8 civarında, pediatrik popülasyonda ise 1000 kişide 108 civarında saptanmıştır (8-10).

Amerikan Diyabet Birliği (ADA), tip 1 diyabetli çocuk ve ergenlerde yılda 100 kişide 1-10 civarında bir DKA riski rapor etmektedir (11). Amerika'da 2002-2010

[1] Uzm. Dr., Trakya Üniversitesi Tıp Fakültesi, Acil Tıp AD., eraycelikturk@gmail.com
[2] Doç. Dr., Trakya Üniversitesi Tıp Fakültesi, Acil Tıp AD., dromersalt@gmail.com

KAYNAKLAR

1. Kitabchi AE, Fisher JN. Insulin therapy of diabetic ketoacidosis: Physiologic versus pharmacologic doses of insulin and their routes of administration. In: Brownlee M, ed. *Handbook of Diabetes Mellitus*. New York: Garland Press; 1981. p. 95–149.
2. Casteels K, Mathieu C. Diabetic ketoacidosis. *Reviews in Endocrine and Metabolic Disorders*. 2003;4(2): 159–66. DOI: 10.1023/A:1022942120000
3. Muneer M, Akbar I. Acute Metabolic Emergencies in Diabetes: DKA, HHS and EDKA. In: Islam S, ed. *Advances in Experimental Medicine and Biology*. Springer, Cham; 2020. p. 85–114. DOI: 10.1007/5584_2020_545
4. Turan T, Karahan İ, Güngüneş A. Diagnostic and therapeutic approach to diabetic ketoacidosis. *Journal of Health Sciences and Medicine*. 2018; 92–8. DOI: 10.32322/jhsm.452023
5. Umpierrez G, Korytkowski M. Diabetic emergencies—ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. *Nature Reviews Endocrinology*. 2016;12(4): 222–32. DOI: 10.1038/nrendo.2016.15
6. Murunga AN, Owira PMO. Diabetic ketoacidosis: an overlooked child killer in sub-Saharan Africa? *Tropical medicine & international health*. 2013;18(11): 1357–64. DOI: 10.1111/tmi.12195
7. Nyenwe EA, Kitabchi AE. The evolution of diabetic ketoacidosis: An update of its etiology, pathogenesis and management. *Metabolism: clinical and experimental*. 2016;65(4): 507–21. DOI: 10.1016/j.metabol.2015.12.007
8. Desai D, Mehta D, Mathias P, et al. Health Care Utilization and Burden of Diabetic Ketoacidosis in the U.S. Over the Past Decade: A Nationwide Analysis. *Diabetes care*. 2018;41(8): 1631–8. DOI: 10.2337/dc17-1379
9. Benoit SR, Zhang Y, Geiss LS, et al. Trends in Diabetic Ketoacidosis Hospitalizations and In-Hospital Mortality - United States, 2000-2014. *MMWR Morbidity and mortality weekly report*. 2018;67(12): 362–5. DOI: 10.15585/mmwr.mm6712a3
10. Li L, Andrews EB, Li X, et al. Incidence of diabetic ketoacidosis and its trends in patients with type 1 diabetes mellitus identified using a U.S. claims database, 2007-2019. *Journal of diabetes and its complications*. 2021;35(7): 107932. DOI: 10.1016/j.jdiacomp.2021.107932
11. Wolfsdorf J, Glaser N, Sperling MA, et al. Diabetic ketoacidosis in infants, children, and adolescents: A consensus statement from the American Diabetes Association. *Diabetes care*. 2006;29(5): 1150–9. DOI: 10.2337/diacare.2951150
12. Dabelea D, Rewers A, Stafford JM, et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study. *Pediatrics*. 2014;133(4): e938–45. DOI: 10.1542/peds.2013-2795
13. Jensen ET, Stafford JM, Saydah S, et al. Increase in Prevalence of Diabetic Ketoacidosis at Diagnosis Among Youth With Type 1 Diabetes: The SEARCH for Diabetes in Youth Study. *Diabetes Care*. 2021;44(7): 1573–8. DOI: 10.2337/dc20-0389
14. Ramphul K, Joynauth J. An Update on the Incidence and Burden of Diabetic Ketoacidosis in the U.S. *Diabetes care*. 2020;43(12): e196–7. DOI: 10.2337/dc20-1258
15. Hirsch IB, Emmett M. Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Epidemiology and pathogenesis [Internet]. *UpToDate*. 2020 [cited 03/15/2020].
16. Unger RH, Orci L. Glucagon and the A cell: physiology and pathophysiology. *The New England journal of medicine*. 1981;304(26): 1575–80. DOI: 10.1056/NEJM198106253042604
17. Diamond MP, Hallarman L, Starick-Zych K, et al. Suppression of counterregulatory hormone response to hypoglycemia by insulin per se. *The Journal of clinical endocrinology and metabolism*. 1991;72(6): 1388–90. DOI: 10.1210/jcem-72-6-1388
18. Philippe J. Insulin regulation of the glucagon gene is mediated by an insulin-responsive DNA element. *Proceedings of the National Academy of Sciences*. 1991;88(16): 7224–7. DOI: 10.1073/pnas.88.16.7224

19. Rose BD, Post TW. Clinical physiology of acid-base and electrolyte disorders. Fifth. New York: McGraw-Hill; 2001.
20. Fayfman M, Pasquel FJ, Umpierrez GE. Management of Hyperglycemic Crises: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State. *The Medical clinics of North America*. 2017;101(3): 587–606. DOI: 10.1016/j.mcna.2016.12.011
21. Miles JM, Haymond MW, Nissen SL, et al. Effects of free fatty acid availability, glucagon excess, and insulin deficiency on ketone body production in postabsorptive man. *The Journal of clinical investigation*. 1983;71(6): 1554–61. DOI: 10.1172/jci110911
22. Cook GA, Nielsen RC, Hawkins RA, et al. Effect of glucagon on hepatic malonyl coenzyme A concentration and on lipid synthesis. *The Journal of biological chemistry*. 1977;252(12): 4421–4.
23. McGarry JD, Woeltje KF, Kuwajima M, et al. Regulation of ketogenesis and the renaissance of carnitine palmitoyltransferase. *Diabetes/metabolism reviews*. 1989;5(3): 271–84. DOI: 10.1002/dmr.5610050305
24. Owen OE, Trapp VE, Skutches CL, et al. Acetone metabolism during diabetic ketoacidosis. *Diabetes*. 1982;31(3): 242–8. DOI: 10.2337/diab.31.3.242
25. Lu J, Zello GA, Randell E, et al. Closing the anion gap: contribution of D-lactate to diabetic ketoacidosis. *Clinica chimica acta; international journal of clinical chemistry*. 2011;412(3–4): 286–91. DOI: 10.1016/j.cca.2010.10.020
26. Arieff AI, Carroll HJ. Nonketotic hyperosmolar coma with hyperglycemia: clinical features, pathophysiology, renal function, acid-base balance, plasma-cerebrospinal fluid equilibria and the effects of therapy in 37 cases. *Medicine*. 1972;51(2): 73–94. DOI: 10.1097/00005792-197203000-00001
27. Katz MA. Hyperglycemia-induced hyponatremia--calculation of expected serum sodium depression. *The New England journal of medicine*. 1973;289(16): 843–4. DOI: 10.1056/NEJM197310182891607
28. Kreisberg RA. Diabetic ketoacidosis: new concepts and trends in pathogenesis and treatment. *Annals of internal medicine*. 1978;88(5): 681–95. DOI: 10.7326/0003-4819-88-5-681
29. Abramson E, Arky R. Diabetic acidosis with initial hypokalemia. Therapeutic implications. *JAMA*. 1966;196(5): 401–3.
30. Adrogué HJ, Lederer ED, Suki WN, et al. Determinants of plasma potassium levels in diabetic ketoacidosis. *Medicine*. 1986;65(3): 163–72. DOI: 10.1097/00005792-198605000-00004
31. DeFronzo RA, Matsuda M. Diabetic ketoacidosis. A combined metabolic-nephrologic approach to therapy. *Diabetes Reviews*. 1994;2(2): 209–38.
32. Kitabchi AE, Wall BM. Management of diabetic ketoacidosis. *American family physician*. 1999;60(2): 455–64.
33. Kitabchi AE, Stentz FB, Umpierrez GE. Diabetic ketoacidosis induces in vivo activation of human T-lymphocytes. *Biochemical and biophysical research communications*. 2004;315(2): 404–7. DOI: 10.1016/j.bbrc.2004.01.065
34. Randall L, Begovic J, Hudson M, et al. Recurrent diabetic ketoacidosis in inner-city minority patients: behavioral, socioeconomic, and psychosocial factors. *Diabetes care*. 2011;34(9): 1891–6. DOI: 10.2337/dc11-0701
35. Wachtel TJ, Silliman RA, Lamberton P. Prognostic factors in the diabetic hyperosmolar state. *Journal of the American Geriatrics Society*. 1987;35(8): 737–41. DOI: 10.1111/j.1532-5415.1987.tb06351.x
36. Lapolla A, Amaro F, Bruttomesso D, et al. Diabetic ketoacidosis: A consensus statement of the Italian Association of Medical Diabetologists (AMD), Italian Society of Diabetology (SID), Italian Society of Endocrinology and Pediatric Diabetoloy (SIEDP). *Nutrition, metabolism, and cardiovascular diseases : NMCD*. 2020;30(10): 1633–44. DOI: 10.1016/j.numecd.2020.06.006
37. Hirsch IB, Emmet M. Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis [Internet]. *UpToDate*. 2022 [cited 03/10/2020].
38. Taylor SI, Blau JE, Rother KI. SGLT2 Inhibitors May Predispose to Ketoacidosis. *The Journal of*

clinical endocrinology and metabolism. 2015;100(8): 2849–52. DOI: 10.1210/jc.2015-1884
39. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS drugs*. 2005;19 Suppl 1: 1–93. DOI: 10.2165/00023210-200519001-00001
40. Warner EA, Greene GS, Buchsbaum MS, et al. Diabetic ketoacidosis associated with cocaine use. *Archives of internal medicine*. 1998;158(16): 1799–802. DOI: 10.1001/archinte.158.16.1799
41. Polonsky WH, Anderson BJ, Lohrer PA, et al. Insulin omission in women with IDDM. *Diabetes care*. 1994;17(10): 1178–85. DOI: 10.2337/diacare.17.10.1178
42. Azkoul A, Sim S, Lawrence V. Diabetic Ketoacidosis in adults: Part 1. Pathogenesis and diagnosis. *South Sudan Medical Journal*. 2022;15(2): 62–6. DOI: 10.4314/ssmj.v15i2.6
43. Daugirdas JT, Kronfol NO, Tzamaloukas AH, et al. Hyperosmolar coma: cellular dehydration and the serum sodium concentration. *Annals of internal medicine*. 1989;110(11): 855–7. DOI: 10.7326/0003-4819-110-11-855
44. Nyenwe EA, Razavi LN, Kitabchi AE, et al. Acidosis: the prime determinant of depressed sensorium in diabetic ketoacidosis. *Diabetes care*. 2010;33(8): 1837–9. DOI: 10.2337/dc10-0102
45. Satman İ, Salman S, İmamoğlu Ş, et al. TEMD Diabetes Mellitus ve Komplikasyonlarının Tanı, Tedavi ve İzlem Kılavuzu.. On ikinci baskı. Ankara: Türkiye Endokrinoloji ve Metabolizma Derneği (TEMD) Yayınları; 2019.
46. Malone ML, Gennis V, Goodwin JS. Characteristics of diabetic ketoacidosis in older versus younger adults. *Journal of the American Geriatrics Society*. 1992;40(11): 1100–4. DOI: 10.1111/j.1532-5415.1992.tb01797.x
47. Umpierrez G, Freire AX. Abdominal pain in patients with hyperglycemic crises. *Journal of critical care*. 2002;17(1): 63–7. DOI: 10.1053/jcrc.2002.33030
48. Gosmanov AR, Gosmanova EO, Kitabchi AE. Hyperglycemic Crises: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State. Feringold KR, Anawalt B, Boyce A, et al., eds. South Dartmouth: MDText.com, Inc.; 2000; 2021.
49. Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. *Diabetes care*. 2009;32(7): 1335–43. DOI: 10.2337/dc09-9032
50. Calimag APP, Chlebek S, Lerma EV, et al. Diabetic ketoacidosis. *Disease-a-month : DM*. 2022; 101418. DOI: 10.1016/j.disamonth.2022.101418
51. Kitabchi AE, Umpierrez GE, Murphy MB, et al. Management of hyperglycemic crises in patients with diabetes. *Diabetes care*. 2001;24(1): 131–53. DOI: 10.2337/diacare.24.1.131
52. Long B, Lentz S, Koyfman A, et al. Euglycemic diabetic ketoacidosis: Etiologies, evaluation, and management. *The American journal of emergency medicine*. 2021;44: 157–60. DOI: 10.1016/j.ajem.2021.02.015
53. 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). DOI: 10.1002/dmrr.2886
54. Lee K, Park IB, Yu SH, et al. Characterization of variable presentations of diabetic ketoacidosis based on blood ketone levels and major society diagnostic criteria: a new view point on the assessment of diabetic ketoacidosis. *Diabetes, metabolic syndrome and obesity : targets and therapy*. 2019;12: 1161–71. DOI: 10.2147/DMSO.S209938
55. Savage MW, Dhatariya KK, Kilvert A, et al. Joint British Diabetes Societies guideline for the management of diabetic ketoacidosis. *Diabetic medicine : a journal of the British Diabetic Association*. 2011;28(5): 508–15. DOI: 10.1111/j.1464-5491.2011.03246.x
56. Porter WH, Yao HH, Karounos DG. Laboratory and clinical evaluation of assays for beta-hydroxybutyrate. *American journal of clinical pathology*. 1997;107(3): 353–8. DOI: 10.1093/ajcp/107.3.353
57. Laffel L. Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. *Diabetes/metabolism research and reviews*. 1999;15(6): 412–26. DOI: 10.1002/(sici)1520-7560(199911/12)15:6<412::aid-dmrr72>3.0.co;2-8

58. Sheikh-Ali M, Karon BS, Basu A, et al. Can serum beta-hydroxybutyrate be used to diagnose diabetic ketoacidosis? *Diabetes care*. 2008;31(4): 643–7. DOI: 10.2337/dc07-1683
59. Smith SW, Manini AF, Szekely T, et al. Bedside detection of urine beta-hydroxybutyrate in diagnosing metabolic acidosis. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine*. 2008;15(8): 751–6. DOI: 10.1111/j.1553-2712.2008.00175.x
60. Bektas F, Eray O, Sari R, et al. Point of Care Blood Ketone Testing of Diabetic Patients in the Emergency Department. *Endocrine Research*. 2004;30(3): 395–402. DOI: 10.1081/ERC-200035231
61. Beck LH. Should the actual or the corrected serum sodium be used to calculate the anion gap in diabetic ketoacidosis? *Cleveland Clinic journal of medicine*. 2001;68(8): 673–4. DOI: 10.3949/ccjm.68.8.673
62. Chambliss AB, Merrill AE. Contemporary Practice in Clinical Chemistry. Fourth Edition. Clarke W, Marzinke M, eds. Elsevier; 2020. 651–663 p. DOI: 10.1016/C2017-0-03060-4
63. Murthy K, Harrington JT, Siegel RD. Profound hypokalemia in diabetic ketoacidosis: a therapeutic challenge. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists*. 2005;11(5): 331–4. DOI: 10.4158/EP.11.5.331
64. Arora S, Cheng D, Wyler B, et al. Prevalence of hypokalemia in ED patients with diabetic ketoacidosis. *The American journal of emergency medicine*. 2012;30(3): 481–4. DOI: 10.1016/j.ajem.2011.01.002
65. Shen T, Braude S. Changes in serum phosphate during treatment of diabetic ketoacidosis: predictive significance of severity of acidosis on presentation. *Internal medicine journal*. 2012;42(12): 1347–50. DOI: 10.1111/imj.12001
66. Kemperman FA, Weber JA, Gorgels J, et al. The influence of ketoacids on plasma creatinine assays in diabetic ketoacidosis. *Journal of internal medicine*. 2000;248(6): 511–7. DOI: 10.1046/j.1365-2796.2000.00768.x
67. Vantyghem MC, Haye S, Balduyck M, et al. Changes in serum amylase, lipase and leukocyte elastase during diabetic ketoacidosis and poorly controlled diabetes. *Acta diabetologica*. 1999;36(1–2): 39–44. DOI: 10.1007/s005920050143
68. Yadav D, Nair S, Norkus EP, et al. Nonspecific hyperamylasemia and hyperlipasemia in diabetic ketoacidosis: incidence and correlation with biochemical abnormalities. *The American journal of gastroenterology*. 2000;95(11): 3123–8. DOI: 10.1111/j.1572-0241.2000.03279.x
69. Stentz FB, Umpierrez GE, Cuervo R, et al. Proinflammatory cytokines, markers of cardiovascular risks, oxidative stress, and lipid peroxidation in patients with hyperglycemic crises. *Diabetes*. 2004;53(8): 2079–86. DOI: 10.2337/diabetes.53.8.2079
70. Nematollahi LR, Taheri E, Larijani B, et al. Catecholamine-Induced Leukocytosis in Acute Hypoglycemic Stress. *Journal of Investigative Medicine* [Internet]. 2007;55(1): S262.
71. Slovis CM, Mork VG, Slovis RJ, et al. Diabetic ketoacidosis and infection: leukocyte count and differential as early predictors of serious infection. *The American journal of emergency medicine*. 1987;5(1): 1–5. DOI: 10.1016/0735-6757(87)90280-4
72. Morris LR, Kitabchi AE. Efficacy of low-dose insulin therapy for severely obtunded patients in diabetic ketoacidosis. *Diabetes care*. 1980;3(1): 53–6. DOI: 10.2337/diacare.3.1.53
73. Handelsman Y, Henry RR, Bloomgarden ZT, et al. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the association of SGLT-2 inhibitors and diabetic ketoacidosis. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists*. 2016;22(6): 753–62. DOI: 10.4158/EP161292.PS
74. Dhatariya K. Blood Ketones: Measurement, Interpretation, Limitations, and Utility in the Management of Diabetic Ketoacidosis. *The review of diabetic studies : RDS*. 2016;13(4): 217–25. DOI: 10.1900/RDS.2016.13.217
75. Dhatariya KK. Defining and characterising diabetic ketoacidosis in adults. *Diabetes research*

and clinical practice. 2019;155: 107797. DOI: 10.1016/j.diabres.2019.107797
76. Wolfsdorf JI, Glaser N, Agus M, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *Pediatric diabetes*. 2018;19 Suppl 27: 155–77. DOI: 10.1111/pedi.12701
77. Heddy N. Guideline for the management of children and young people under the age of 18 years with diabetic ketoacidosis (British Society for Paediatric Endocrinology and Diabetes). *Archives of disease in childhood Education and practice edition*. 2021;106(4): 220–2. DOI: 10.1136/archdischild-2020-320076
78. Kitabchi AE, Nyenwe EA. Hyperglycemic crises in diabetes mellitus: diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Endocrinology and metabolism clinics of North America*. 2006;35(4): 725–51, viii. DOI: 10.1016/j.ecl.2006.09.006
79. McGuire LC, Cruickshank AM, Munro PT. Alcoholic ketoacidosis. *Emergency medicine journal*. 2006;23(6): 417–20. DOI: 10.1136/emj.2004.017590
80. Cahill GF. Fuel metabolism in starvation. *Annual review of nutrition*. 2006;26: 1–22. DOI: 10.1146/annurev.nutr.26.061505.111258
81. Evans K. Diabetic ketoacidosis: update on management. *Clinical medicine (London, England)*. 2019;19(5): 396–8. DOI: 10.7861/clinmed.2019-0284
82. Roumelioti ME, Sun Y, Ganta K, et al. Management of extracellular volume in patients with end-stage kidney disease and severe hyperglycemia. *Journal of diabetes and its complications*. 2020;34(8): 107615. DOI: 10.1016/j.jdiacomp.2020.107615
83. Galindo RJ, Pasquel FJ, Fayfman M, et al. Clinical characteristics and outcomes of patients with end-stage renal disease hospitalized with diabetes ketoacidosis. *BMJ open diabetes research & care*. 2020;8(1). DOI: 10.1136/bmjdrc-2019-000763
84. Blicker J, Herd AM, Talbot J. Diabetic ketoacidosis in the dialysis-dependent patient: two case reports and recommendations for treatment. *CJEM*. 2004;6(4): 281–4. DOI: 10.1017/s1481803500009271
85. Sun Y, Roumelioti ME, Ganta K, et al. Dialysis-associated hyperglycemia: manifestations and treatment. *International urology and nephrology*. 2020;52(3): 505–17. DOI: 10.1007/s11255-019-02373-1
86. Nyenwe EA, Kitabchi AE. Evidence-based management of hyperglycemic emergencies in diabetes mellitus. *Diabetes research and clinical practice*. 2011;94(3): 340–51. DOI: 10.1016/j.diabres.2011.09.012
87. Praveen PA, Hockett CW, Ong TC, et al. Diabetic ketoacidosis at diagnosis among youth with type 1 and type 2 diabetes: Results from SEARCH (United States) and YDR (India) registries. *Pediatric diabetes*. 2021;22(1): 40–6. DOI: 10.1111/pedi.12979
88. Kraut JA, Madias NE. Treatment of acute metabolic acidosis: a pathophysiologic approach. *Nature reviews Nephrology*. 2012;8(10): 589–601. DOI: 10.1038/nrneph.2012.186
89. Middleton P, Kelly AM, Brown J, et al. Agreement between arterial and central venous values for pH, bicarbonate, base excess, and lactate. *Emergency medicine journal : EMJ*. 2006;23(8): 622–4. DOI: 10.1136/emj.2006.035915
90. Loh TP, Saw S, Sethi SK. Bedside monitoring of blood ketone for management of diabetic ketoacidosis: proceed with care. *Diabetic medicine : a journal of the British Diabetic Association*. 2012;29(6): 827–8. DOI: 10.1111/j.1464-5491.2011.03490.x
91. Hirsch IB, Emmet M. Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Treatment [Internet]. *UpToDate*. 2022 [cited 03/10/2020].
92. Reddy PK, Kuchay MS, Mehta Y, et al. Diabetic ketoacidosis precipitated by COVID-19: A report of two cases and review of literature. *Diabetes & metabolic syndrome*. 2020;14(5): 1459–62. DOI: 10.1016/j.dsx.2020.07.050
93. Yang JK, Lin SS, Ji XJ, 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
94. Pal R, Banerjee M, Yadav U, et al. Clinical profile and outcomes in COVID-19 patients with dia-

betic ketoacidosis: A systematic review of literature. *Diabetes & metabolic syndrome*. 2020;14(6): 1563–9. DOI: 10.1016/j.dsx.2020.08.015

95. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet (London, England)*. 2020;395(10236): 1569–78. DOI: 10.1016/S0140-6736(20)31022-9
96. Rayman G, Lumb A, Kennon B, et al. Guidance on the management of Diabetic Ketoacidosis in the exceptional circumstances of the COVID-19 pandemic. *Diabetic medicine : a journal of the British Diabetic Association*. 2020;37(7): 1214–6. DOI: 10.1111/dme.14328
97. Palermo NE, Sadhu AR, McDonnell ME. Diabetic Ketoacidosis in COVID-19: Unique Concerns and Considerations. *The Journal of clinical endocrinology and metabolism*. 2020;105(8). DOI: 10.1210/clinem/dgaa360
98. Priyambada L, Wolfsdorf JI, Brink SJ, et al. ISPAD Clinical Practice Consensus Guideline: Diabetic ketoacidosis in the time of COVID-19 and resource-limited settings-role of subcutaneous insulin. *Pediatric diabetes*. 2020;21(8): 1394–402. DOI: 10.1111/pedi.13118