

GENERAL INTERNAL MEDICINE

Editor

Ali Kemal KADIROĞLU

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PREFACE

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Chapter 1

EFFECT OF COVID-19 PANDEMIC ON DIABETES MELLITUS AND IT'S COMPLICATIONS IN CHILDREN AND ADULTS

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INTRODUCTION

In the last days of December 2019, an increase in cases of severe pneumonia was detected in Wuhan, China. At the end of the investigations, the pathogen in these patients was found to be similar to SARS coronavirus, so the pathogen was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease was named coronavirus disease 2019 (COVID -19). The COVID -19 disease spread all over the world in a short time, after which the World Health Organization declared the state of a pandemic on March 11, 2020 (1). By the end of the 10th month of the pandemic, the COVID -19 disease had spread to 89.8 million people and resulted in the death of 1.93 people around the world (2).

Coronavirus

Of the hundreds of coronavirus types, only seven are known to cause disease in humans; four of these (NL63, HKU1, OC43, and E229) are seasonal influenza factors, and the others are severe acute respiratory syndrome (SARS-CoV), Middle East respiratory syndrome (MERS), and SARS-CoV-2 (3). SARS-CoV-2 virus is mainly transmitted by droplets, but the virus has also been sighted in the feces and urine of affected individuals, so the possibility of transmission by other routes should not be ruled out (4). Coronaviruses have crown-like spike proteins on their surface that facilitate their entry into host cells. These proteins of SARS-CoV-2 are thought to interact with angiotensin-converting enzyme 2 (ACE2) receptors

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it is generally recommended that they eat a healthy diet, exercise regularly, do not smoke, and keep their blood pressure and HbA1c levels within normal limits (101-103,140).

Cardiovascular Diseases

Cardiovascular diseases are the most important causes of morbidity and mortality in patients with DM (128). On the other hand, SARS-CoV-2 infection has a more severe course in patients with cardiovascular disease. This virus can have a direct cytotoxic effect on vascular endothelial cells because of its ACE2 receptor. On the other hand, SARS-CoV-2 virus may indirectly affect the cardiovascular system through increased sympathetic stimulation, inflammation-induced cytokine storm, and increased tendency for coagulation. As a result of all these effects, COVID -19 increases the risk of myocardial infarction, myocarditis, heart failure, venous thromboembolism, and arrhythmia (141). These tables significantly increase mortality from SARS-CoV-2 infection (42).

A meta-analysis showed that the presence of cardiovascular disease increases the likelihood of developing severe COVID -19 disease or requiring intensive care unit treatment by up to 3-fold (142). On the other hand, it was observed that cardiovascular disease was detected more than 2.5 times in those who died in the ICU because of this disease (53% vs. 20%) (143). Treatment of obesity, dyslipidemia and hypertension is important to prevent cardiovascular disease.

As a result, individuals with DM are at high risk during the pandemic for both SARS-CoV-2 virus infection and associated complications. It is very important to detect these conditions early and take preventive measures against them to avoid the poor prognosis they may cause.

REFERENCES

1. WHO. IHR Emergency Committee on Novel Coronavirus (2019-nCoV). Geneva, Switzerland. 2020.
2. WHO. WHO Coronavirus Disease (COVID-19) Dashboard. 2021.
3. Liu DX, Liang JQ, Fung TS. Human Coronavirus-229E, -OC43, -NL63, and -HKU1. In: Reference Module in Life Sciences (Internet). Elsevier; 2020 (cited 2020 Dec 17). Available from: / pmc/articles/PMC7204879/?report=abstract
4. Rio C, Malani PN. COVID-19—New Insights on a Rapidly Changing Epidemic. JAMA (Internet). 2020 Apr 14;323(14):1339. Available from: <https://jamanetwork.com/journals/jama/fullarticle/2762510>
5. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;
6. Redd WD, Zhou JC, Hathorn KE, McCarty TR, Bazarbashi AN, Thompson CC, et al. Prevalence and Characteristics of Gastrointestinal Symptoms in Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection in the United States: A Multicenter Cohort Study. Gastro-

- enterology (Internet). 2020 Aug;159(2):765-767.e2. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0016508520305643>
7. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First Case of 2019 Novel Coronavirus in the United States. *N Engl J Med* (Internet). 2020 Mar 5;382(10):929–36. Available from: <http://www.nejm.org/doi/10.1056/NEJMoa2001191>
 8. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA* (Internet). 2020 Mar 17;323(11):1061. Available from: <https://jamanetwork.com/journals/jama/fullarticle/2761044>
 9. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* (Internet). 2020 Feb;395(10223):507–13. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0140673620302117>
 10. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. *Gastroenterology* (Internet). 2020 May;158(6):1831-1833.e3. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0016508520302821>
 11. Cheung KS, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, et al. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis. *Gastroenterology* (Internet). 2020 Jul;159(1):81–95. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0016508520304480>
 12. Yeo C, Kaushal S, Yeo D. Enteric involvement of coronaviruses: is faecal–oral transmission of SARS-CoV-2 possible? *Lancet Gastroenterol Hepatol* (Internet). 2020 Apr;5(4):335–7. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S2468125320300480>
 13. Gu J, Han B, Wang J. COVID-19: Gastrointestinal Manifestations and Potential Fecal–Oral Transmission. *Gastroenterology* (Internet). 2020 May;158(6):1518–9. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S001650852030281X>
 14. Li Y, Bai W, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol* (Internet). 2020 Jun 11;92(6):552–5. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25728>
 15. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, et al. Virology, Epidemiology, Pathogenesis, and Control of COVID-19. *Viruses* (Internet). 2020 Mar 27;12(4):372. Available from: <https://www.mdpi.com/1999-4915/12/4/372>
 16. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. Gallagher T, editor. *J Virol* (Internet). 2020 Jan 29;94(7). Available from: <https://jvi.asm.org/content/94/7/e00127-20>
 17. Wu Y, Chen C, Chan Y. The outbreak of COVID-19: An overview. *J Chinese Med Assoc.* 2020;83(3):217–20.
 18. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun* (Internet). 2020 May;109:102433. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0896841120300469>
 19. Gudbjartsson DF, Helgason A, Jonsson H, Magnusson OT, Melsted P, Norddahl GL, et al. Spread of SARS-CoV-2 in the Icelandic Population. *N Engl J Med.* 2020;
 20. Rosenberg ES, Dufort EM, Blog DS, Hall EW, Hoefler D, Backenson BP, et al. COVID-19 Testing, Epidemic Features, Hospital Outcomes, and Household Prevalence, New York State–March 2020. *Clin Infect Dis.* 2020;
 21. Lavezzo E, Franchin E, Ciavarella C, Cuomo-Dannenburg G, Barzon L, Del Vecchio C, et al. Suppression of a SARS-CoV-2 outbreak in the Italian municipality of Vo'. *Nature.* 2020;
 22. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020;
 23. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China. *JAMA.* 2020;

24. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 Among Children in China. *Pediatrics* (Internet). 2020 Jun;145(6):e20200702. Available from: <http://pediatrics.aappublications.org/lookup/doi/10.1542/peds.2020-0702>
25. Tian S, Hu N, Lou J, Chen K, Kang X, Xiang Z, et al. Characteristics of COVID-19 infection in Beijing. *J Infect*. 2020;
26. Pairo-Castineira E, Clohisey S, Klaric L, Bretherick AD, Rawlik K, Pasko D, et al. Genetic mechanisms of critical illness in Covid-19. *Nature* (Internet). 2020 Dec 11; Available from: <http://www.nature.com/articles/s41586-020-03065-y>
27. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: Prospective observational cohort study. *BMJ*. 2020;
28. Swann O, Holden K, Turtle L, Pollock L, Fairfield C, Drake T, et al. Clinical characteristics of children and young people hospitalised with covid-19 in the United Kingdom: prospective multicentre observational cohort study. *BMJ*. 2020;
29. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected with SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA - J Am Med Assoc*. 2020;
30. Johns Hopkins University. COVID-19 Map - Johns Hopkins Coronavirus Resource Center. Johns Hopkins Coronavirus Resource Center. 2020.
31. Bialek S, Gierke R, Hughes M, McNamara LA, Pilishvili T, Skoff T. Coronavirus Disease 2019 in Children — United States, February 12–April 2, 2020. *MMWR Morb Mortal Wkly Rep* (Internet). 2020 Apr 10;69(14):422–6. Available from: http://www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm?s_cid=mm6914e4_w
32. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 Infection in Children. *N Engl J Med* (Internet). 2020 Apr 23;382(17):1663–5. Available from: <http://www.nejm.org/doi/10.1056/NEJMc2005073>
33. Lee PI, Hu YL, Chen PY, Huang YC, Hsueh PR. Are children less susceptible to COVID-19? *J Microbiol Immunol Infect*. 2020;
34. Nickbakhsh S, Mair C, Matthews L, Reeve R, Johnson PCD, Thorburn F, et al. Virus-virus interactions impact the population dynamics of influenza and the common cold. *Proc Natl Acad Sci U S A*. 2019;
35. Bunyavanich S, Do A, Vicencio A. Nasal Gene Expression of Angiotensin-Converting Enzyme 2 in Children and Adults. *JAMA - Journal of the American Medical Association*. 2020.
36. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract*. 2019;
37. Zylke JW, DeAngelis CD. Pediatric chronic diseases - Stealing childhood. *Journal of the American Medical Association*. 2007.
38. Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, et al. Incidence Trends of Type 1 and Type 2 Diabetes among Youths, 2002–2012. *N Engl J Med*. 2017;
39. Iglay K, Hannachi H, Howie PJ, Xu J, Li X, Engel SS, et al. Prevalence and co-prevalence of comorbidities among patients with type 2 diabetes mellitus. *Curr Med Res Opin*. 2016;
40. Long AN, Dagogo-Jack S. Comorbidities of Diabetes and Hypertension: Mechanisms and Approach to Target Organ Protection. *Journal of Clinical Hypertension*. 2011.
41. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* (Internet). 2020 Feb;395(10223):497–506. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0140673620301835>
42. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;
43. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. *JAMA Pediatr*. 2020;

44. Kumar Nathella P, Babu S. Influence of diabetes mellitus on immunity to human tuberculosis. *Immunology (Internet)*. 2017 Sep;152(1):13–24. Available from: <http://doi.wiley.com/10.1111/imm.12762>
45. Xu M, Liu PP, Li H. Innate Immune Signaling and Its Role in Metabolic and Cardiovascular Diseases. *Physiol Rev (Internet)*. 2019 Jan 1;99(1):893–948. Available from: <https://www.physiology.org/doi/10.1152/physrev.00065.2017>
46. Bode B, Garrett V, Messler J, McFarland R, Crowe J, Booth R, et al. Glycemic Characteristics and Clinical Outcomes of COVID-19 Patients Hospitalized in the United States. *J Diabetes Sci Technol (Internet)*. 2020 Jul 9;14(4):813–21. Available from: <http://journals.sagepub.com/doi/10.1177/1932296820924469>
47. Yang J-K, Lin S-S, Ji X-J, Guo L-M. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol (Internet)*. 2010 Sep;47(3):193–9. Available from: <http://link.springer.com/10.1007/s00592-009-0109-4>
48. Roca-Ho H, Riera M, Palau V, Pascual J, Soler M. Characterization of ACE and ACE2 Expression within Different Organs of the NOD Mouse. *Int J Mol Sci (Internet)*. 2017 Mar 5;18(3):563. Available from: <http://www.mdpi.com/1422-0067/18/3/563>
49. Bornstein SR, Dalan R, Hopkins D, Mingrone G, Boehm BO. Endocrine and metabolic link to coronavirus infection. *Nature Reviews Endocrinology*. 2020.
50. Bindom SM, Lazartigues E. The sweeter side of ACE2: Physiological evidence for a role in diabetes. *Molecular and Cellular Endocrinology*. 2009.
51. Morigi M, Angioletti S, Imberti B, Donadelli R, Micheletti G, Figliuzzi M, et al. Leukocyte-endothelial interaction is augmented by high glucose concentrations and hyperglycemia in a NF- κ B-dependent fashion. *J Clin Invest (Internet)*. 1998 May 1;101(9):1905–15. Available from: <http://www.jci.org/articles/view/656>
52. Kassir R. Risk of COVID-19 for patients with obesity. *Obes Rev (Internet)*. 2020 Jun 13;21(6). Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1111/obr.13034>
53. Szymczak-Pajor I, Śliwińska A. Analysis of Association between Vitamin D Deficiency and Insulin Resistance. *Nutrients (Internet)*. 2019 Apr 6;11(4):794. Available from: <https://www.mdpi.com/2072-6643/11/4/794>
54. Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. *J Endocrinol Invest (Internet)*. 2020 Jun 28;43(6):867–9. Available from: <http://link.springer.com/10.1007/s40618-020-01236-2>
55. Guan W, Liang W, Zhao Y, Liang H, Chen Z, Li Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J (Internet)*. 2020 May;55(5):2000547. Available from: <http://erj.ersjournals.com/lookup/doi/10.1183/13993003.00547-2020>
56. Pal R, Bhadada SK. COVID-19 and diabetes mellitus: An unholy interaction of two pandemics. *Diabetes Metab Syndr Clin Res Rev (Internet)*. 2020 Jul;14(4):513–7. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1871402120301144>
57. Liu W, Hualan L. COVID-19: Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Heme Metabolism. *ChemRxiv Prepr Serv Chem (Internet)*. 2020; Available from: chemrxiv.org/articles/COVID-19_Disease_ORF8_and_Surface_Glycoprotein_Inhibit_Heme_Metabolism_by_Binding_to_Porphyrin/11938173/5;2020
58. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis (Internet)*. 2020 Jul 28;71(15):762–8. Available from: <https://academic.oup.com/cid/article/71/15/762/5803306>
59. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev (Internet)*. 2020 Oct 7;36(7). Available from: <https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3319>
60. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. *Clin Immunol (Internet)*. 2020 May;214:108393. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1521661620301984>

61. Guo Y-R, Cao Q-D, Hong Z-S, Tan Y-Y, Chen S-D, Jin H-J, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. *Mil Med Res* (Internet). 2020 Dec 13;7(1):11. Available from: <https://mmrjournal.biomedcentral.com/articles/10.1186/s40779-020-00240-0>
62. Hussain A, Bhowmik B, do Vale Moreira NC. COVID-19 and diabetes: Knowledge in progress. *Diabetes Res Clin Pract* (Internet). 2020 Apr;162:108142. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0168822720303922>
63. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *The Lancet*. 2020.
64. Vazquez-Garza E, Jerjes-Sanchez C, Navarrete A, Joya-Harrison J, Rodriguez D. Venous thromboembolism: thrombosis, inflammation, and immunothrombosis for clinicians. *Journal of Thrombosis and Thrombolysis*. 2017.
65. Teuwen L-A, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. *Nat Rev Immunol*. 2020;20:389–91.
66. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak, Yelena et al. Factors associated with hospitalization and critical illness among 4,103 patients with Covid-19 disease in New York City. *BMJ*. 2020;
67. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes among 5700 Patients Hospitalized with COVID-19 in the New York City Area. *JAMA - J Am Med Assoc*. 2020;
68. Zhu L, She Z-G, Cheng X, Qin J-J, Zhang X-J, Cai J, et al. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metab* (Internet). 2020 Jun;31(6):1068-1077.e3. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1550413120302382>
69. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *JAMA - Journal of the American Medical Association*. 2020.
70. Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol* (Internet). 2020 Oct;8(10):813–22. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S2213858720302722>
71. Pal R, Bhansali A. COVID-19, diabetes mellitus and ACE2: The conundrum. *Diabetes Res Clin Pract* (Internet). 2020 Apr;162:108132. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S016882272030382X>
72. Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. *Diabetes Metab Syndr Clin Res Rev*. 2020;
73. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia – A systematic review, meta-analysis, and meta-regression: Diabetes and COVID-19. *Diabetes Metab Syndr Clin Res Rev*. 2020;
74. Pal R, Bhadada SK. COVID-19 and non-communicable diseases. *Postgraduate Medical Journal*. 2020.
75. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, et al. Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with Mortality among Patients with Hypertension Hospitalized with COVID-19. *Circ Res*. 2020;
76. Opal SM, Girard TD, Ely EW. The immunopathogenesis of sepsis in elderly patients. In: *Clinical Infectious Diseases*. 2005.
77. Gupta R, Ghosh A, Singh AK, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. *Diabetes Metab Syndr Clin Res Rev* (Internet). 2020 May;14(3):211–2. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1871402120300424>
78. Benhalima K, Song SH, Wilmot EG, Khunti K, Gray LJ, Lawrence I, et al. Characteristics, complications and management of a large multiethnic cohort of younger adults with type 2 diabetes. *Prim Care Diabetes* (Internet). 2011 Dec;5(4):245–50. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1751991811000519>

79. Pinhas-Hamiel O, Zeitler P. Acute and chronic complications of type 2 diabetes mellitus in children and adolescents. *Lancet* (Internet). 2007 May;369(9575):1823–31. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0140673607608216>
80. Copeland KC, Zeitler P, Geffner M, Guandalini C, Higgins J, Hirst K, et al. Characteristics of Adolescents and Youth with Recent-Onset Type 2 Diabetes: The TODAY Cohort at Baseline. *J Clin Endocrinol Metab* (Internet). 2011 Jan;96(1):159–67. Available from: <https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2010-1642>
81. Berge LI, Riise T, Fasmer OB, Lund A, Oedegaard KJ, Hundal Ø. Risk of depression in diabetes is highest for young persons using oral anti-diabetic agents. *Diabet Med* (Internet). 2012 Apr;29(4):509–14. Available from: <http://doi.wiley.com/10.1111/j.1464-5491.2011.03530.x>
82. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* (Internet). 2005 Jan;365(9455):217–23. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0140673605177411>
83. Din-Dzietham R, Liu Y, Bielo M-V, Shamsa F. High Blood Pressure Trends in Children and Adolescents in National Surveys, 1963 to 2002. *Circulation* (Internet). 2007 Sep 25;116(13):1488–96. Available from: <https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.106.683243>
84. Hansen ML, Gunn PW, Kaelber DC. Underdiagnosis of Hypertension in Children and Adolescents. *JAMA* (Internet). 2007 Aug 22;298(8):874. Available from: <http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.298.8.874>
85. Cheung EL, Bell CS, Samuel JP, Poffenbarger T, Redwine KM, Samuels JA. Race and Obesity in Adolescent Hypertension. *Pediatrics* (Internet). 2017 May;139(5):e20161433. Available from: <http://pediatrics.aappublications.org/lookup/doi/10.1542/peds.2016-1433>
86. Williams CL, Hayman LL, Daniels SR, Robinson TN, Steinberger J, Paridon S, et al. Cardiovascular Health in Childhood. *Circulation* (Internet). 2002 Jul 2;106(1):143–60. Available from: <https://www.ahajournals.org/doi/10.1161/01.CIR.0000019555.61092.9E>
87. Inge TH, King WC, Jenkins TM, Courcoulas AP, Mitsnefes M, Flum DR, et al. The Effect of Obesity in Adolescence on Adult Health Status. *Pediatrics* (Internet). 2013 Dec 1;132(6):1098–104. Available from: <http://pediatrics.aappublications.org/cgi/doi/10.1542/peds.2013-2185>
88. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of Obesity Among Adults and Youth: United States, 2015–2016. *NCHS Data Brief*. 2017;(288):1–8.
89. Vogt BA. Hypertension in children and adolescents: definition, pathophysiology, risk factors, and long-term sequelae. *Curr Ther Res* (Internet). 2001 Apr;62(4):283–97. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0011393X01800138>
90. Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. *J Med Virol* (Internet). 2020 Jul;92(7):797–806. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25783>
91. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* (Internet). 2020 Apr;8(4):e21. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S2213260020301168>
92. Chen Y, Gong X, Wang L, Guo J. Effects of hypertension, diabetes and coronary heart disease on COVID-19 diseases severity: a systematic review and meta-analysis. *MedRxiv*. 2020;
93. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis* (Internet). 2020 May;94:91–5. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1201971220301363>
94. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* (Internet). 2020 Jul 1;180(7):934. Available from: <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2763184>
95. Chalmers JD, Singanayagam A, Hill AT. Systolic blood pressure is superior to other haemodynamic predictors of outcome in community acquired pneumonia. *Thorax* (Internet). 2008 Aug 1;63(8):698–702. Available from: <https://thorax.bmj.com/lookup/doi/10.1136/thx.2008.095562>

96. Price LC, Wort SJ. Pulmonary hypertension in ARDS: inflammation matters! *Thorax* (Internet). 2017 May;72(5):396–7. Available from: <https://thorax.bmj.com/lookup/doi/10.1136/thoraxjnl-2016-209199>
97. Dai Q, Wang S, Liu R, Wang H, Zheng J, Yu K. Risk factors for outcomes of acute respiratory distress syndrome patients: a retrospective study. *J Thorac Dis* (Internet). 2019 Mar;11(3):673–85. Available from: <http://jtd.amegroups.com/article/view/27663/20447>
98. Tikellis C, Thomas MC. Angiotensin-Converting Enzyme 2 (ACE2) Is a Key Modulator of the Renin Angiotensin System in Health and Disease. *Int J Pept* (Internet). 2012 Mar 20;2012:1–8. Available from: <https://www.hindawi.com/journals/ijpep/2012/256294/>
99. Bozkurt B, Kovacs R, Harrington B. HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19. *Am Coll Cardiol* (Internet). 2020; Available from: https://professional.heart.org/professional/ScienceNews/UCM_505836_HFSAACCAHA-statement-addresses-concerns-re-using-RAAS-antagonists-in-COVID-19.jsp
100. Hill MA, Mantzoros C, Sowers JR. Commentary: COVID-19 in patients with diabetes. *Metabolism* (Internet). 2020 Jun;107:154217. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0026049520300810>
101. Mente A, de Koning L, Shannon HS, Anand SS. A Systematic Review of the Evidence Supporting a Causal Link Between Dietary Factors and Coronary Heart Disease. *Arch Intern Med* (Internet). 2009 Apr 13;169(7):659. Available from: <http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinternmed.2009.38>
102. Rigotti NA, Clair C. Managing tobacco use: the neglected cardiovascular disease risk factor. *Eur Heart J* (Internet). 2013 Nov 2;34(42):3259–67. Available from: <https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/eh352>
103. Alves AJ, Viana JL, Cavalcante SL, Oliveira NL, Duarte JA, Mota J, et al. Physical activity in primary and secondary prevention of cardiovascular disease: Overview updated. *World J Cardiol* (Internet). 2016;8(10):575. Available from: <http://www.wjgnet.com/1949-8462/full/v8/i10/575.htm>
104. World Health Organization. *Global Report on Diabetes*. Isbn. 2016;
105. Centers for Disease Control and Prevention website. *Centers for Disease Control and Prevention Overweight and obesity*. 2012.
106. Ogden CL. Prevalence of High Body Mass Index in US Children and Adolescents, 2007–2008. *JAMA* (Internet). 2010 Jan 20;303(3):242. Available from: <http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2009.2012>
107. Whitlock G, Lewington S, Sherliker P, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* (Internet). 2009 Mar;373(9669):1083–96. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0140673609603184>
108. Cai Q, Chen F, Wang T, Luo F, Liu X, Wu Q, et al. Obesity and COVID-19 Severity in a Designated Hospital in Shenzhen, China. *Diabetes Care*. 2020;
109. Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia*. 2020;
110. Rahmouni K, Correia MLG, Haynes WG, Mark AL. Obesity-Associated Hypertension. *Hypertension* (Internet). 2005 Jan;45(1):9–14. Available from: <https://www.ahajournals.org/doi/10.1161/01.HYP.0000151325.83008.b4>
111. Kotsis V, Stabouli S, Papakatsika S, Rizos Z, Parati G. Mechanisms of obesity-induced hypertension. *Hypertension Research*. 2010.
112. Pickup JC, Mattock MB, Chusney GD, Burt D. NIDDM as a disease of the innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. *Diabetologia*. 1997;Rahmouni K, Correia MLG, Haynes WG, Mark AL. Obesity-Associated Hypertension. *Hypertension* (Internet). 2005 Jan;45(1):9–14. Available from: <https://www.ahajournals.org/doi/10.1161/01.HYP.0000151325.83008.b4>

113. Pickup JC, Crook MA. Is type II diabetes mellitus a disease of the innate immune system? *Diabetologia*. 1998.
114. Hu FB, Stampfer MJ. Insulin Resistance and Hypertension. *Circulation (Internet)*. 2005 Sep 20;112(12):1678–80. Available from: <https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.105.568055>
115. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. *Journal of Clinical Investigation*. 2005.
116. Shoelson SE, Herrero L, Naaz A. Obesity, Inflammation, and Insulin Resistance. *Gastroenterology*. 2007;
117. Pickup JC. Inflammation and Activated Innate Immunity in the Pathogenesis of Type 2 Diabetes. *Diabetes Care*. 2004.
118. Medzhitov R, Janeway C. Innate Immunity. Mackay IR, Rosen FS, editors. *N Engl J Med (Internet)*. 2000 Aug 3;343(5):338–44. Available from: <http://www.nejm.org/doi/10.1056/NEJM200008033430506>
119. Hibbert K, Rice M, Malhotra A. Obesity and ARDS. *Chest (Internet)*. 2012 Sep;142(3):785–90. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0012369212605261>
120. Murugan A, Sharma G. Obesity and respiratory diseases. *Chron Respir Dis (Internet)*. 2008 Nov;5(4):233–42. Available from: <http://journals.sagepub.com/doi/10.1177/1479972308096978>
121. Jeevanandam M, Young DH, Schiller WR. Obesity and the metabolic response to severe multiple trauma in man. *J Clin Invest (Internet)*. 1991 Jan 1;87(1):262–9. Available from: <http://www.jci.org/articles/view/114980>
122. Ridley EJ, Tierney A, King S, Ainslie E, Udy A, Scheinkestel C, et al. Measured Energy Expenditure Compared With Best-Practice Recommendations for Obese, Critically Ill Patients—A Prospective Observational Study. *J Parenter Enter Nutr (Internet)*. 2020 Aug 6;44(6):1144–9. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/jpen.1791>
123. Borel AL, Schwebel C, Planquette B, Vésin A, Garrouste-Orgeas M, Adrie C, et al. Initiation of nutritional support is delayed in critically ill obese patients: a multicenter cohort study. *Am J Clin Nutr (Internet)*. 2014 Sep 1;100(3):859–66. Available from: <https://academic.oup.com/ajcn/article/100/3/859/4576502>
124. Thibault R, Seguin P, Tamion F, Pichard C, Singer P. Nutrition of the COVID-19 patient in the intensive care unit (ICU): a practical guidance. *Crit Care (Internet)*. 2020 Dec 19;24(1):447. Available from: <https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-03159-z>
125. Walsh NP, Gleeson M, Shephard RJ, Gleeson M, Woods JA, Bishop NC et al. Position statement. Part one: immune function and exercise. *Exerc Immunol Rev*. 2011;17:6–63.
126. Szlezak AM, Szlezak SL, Keane J, Tajouri L, Minahan C. Establishing a dose-response relationship between acute resistance-exercise and the immune system: Protocol for a systematic review. *Immunol Lett (Internet)*. 2016 Dec;180:54–65. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0165247816302437>
127. Taskinen M, Boren J. New insights into the pathophysiology of dyslipidemia in type 2 diabetes. *Atherosclerosis*. 2015;239:483–495.
128. Wang CCL, Hess CN, Hiatt WR, Goldfine AB. Clinical Update: Cardiovascular Disease in Diabetes Mellitus. *Circulation (Internet)*. 2016 Jun 14;133(24):2459–502. Available from: <https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.116.022194>
129. Weinstock RS, Caprio S, Copeland KC, et al. Lipid and inflammatory cardiovascular risk worsens over 3 years in youth with type 2 diabetes: the TODAY clinical trial. *Diabetes Care*. 2013;36(6):1758–64.
130. Tall AR, Laurent YC. Cholesterol, inflammation and innate immunity. *Nat Rev Immunol*. 2015;15(2):104–16.
131. Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clin Rheumatol*. 2020;39(7):2085–94.
132. Hidesuke Kaji. High-density lipoproteins and the immune system. *J Lipids*. 2013;2013:684903.

133. McKechnie JL, Blish CA. The Innate Immune System: Fighting on the Front Lines or Fanning the Flames of COVID-19? *Cell Host Microbe* (Internet). 2020 Jun;27(6):863–9. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1931312820302912>
134. Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C, Zuñiga FA. Association between insulin resistance and the development of cardiovascular disease. *Cardiovasc Diabetol* (Internet). 2018 Dec 31;17(1):122. Available from: <https://cardiab.biomedcentral.com/articles/10.1186/s12933-018-0762-4>
135. Zheng S, Xu H, Zhou H, Ren X, Han T, Chen Y, et al. Associations of lipid profiles with insulin resistance and β cell function in adults with normal glucose tolerance and different categories of impaired glucose regulation. Wang G, editor. *PLoS One* (Internet). 2017 Feb 15;12(2):e0172221. Available from: <https://dx.plos.org/10.1371/journal.pone.0172221>
136. Kim J, Montagnani M, Chandrasekran S, Quon MJ. Role of Lipotoxicity in Endothelial Dysfunction. *Heart Fail Clin* (Internet). 2012 Oct;8(4):589–607. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1551713612000700>
137. Frolidi G, Dorigo P. Endothelial dysfunction in Coronavirus disease 2019 (COVID-19): Gender and age influences. *Med Hypotheses* (Internet). 2020 Nov;144:110015. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0306987720315334>
138. Olejnik J, Hume AJ, Mühlberger E. Toll-like receptor 4 in acute viral infection: Too much of a good thing. Dutch RE, editor. *PLOS Pathog* (Internet). 2018 Dec 20;14(12):e1007390. Available from: <https://dx.plos.org/10.1371/journal.ppat.1007390>
139. Hariyanto TI, Kurniawan A. Dyslipidemia is associated with severe coronavirus disease 2019 (COVID-19) infection. *Diabetes Metab Syndr Clin Res Rev* (Internet). 2020 Sep;14(5):1463–5. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1871402120303027>
140. Charlton-Menys V, Betteridge DJ, Colhoun H, Fuller J, France M, Hitman GA, et al. Targets of Statin Therapy: LDL Cholesterol, Non-HDL Cholesterol, and Apolipoprotein B in Type 2 Diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS). *Clin Chem* (Internet). 2009 Mar 1;55(3):473–80. Available from: <https://academic.oup.com/clinchem/article/55/3/473/5631731>
141. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System. *JAMA Cardiol* (Internet). 2020 Jul 1;5(7):831. Available from: <https://jamanetwork.com/journals/jamacardiology/fullarticle/2763846>
142. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol* (Internet). 2020 May 11;109(5):531–8. Available from: <http://link.springer.com/10.1007/s00392-020-01626-9>
143. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* (Internet). 2020 May;8(5):475–81. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S2213260020300795>

Chapter 2

EVALUATING CHRONIC OBSTRUCTIVE LUNG DISEASE WITH CURRENT GUIDELINES

Burak DEMİRÇİ¹

INTRODUCTION AND EPIDEMIOLOGY

Chronic Obstructive Pulmonary Disease (COPD) is the third most common cause of death in the world and is a progressive disease with exacerbations, mortality is 4-30%. This disease is also closely related to severe morbidity and impaired quality of life (1,2). COPD is characterized by persistent progressive airway stenosis as a result of the chronic inflammatory response of the lungs and airways to harmful gases and particles. The course of the disease is in the form of exacerbations. Episodes of exacerbation and comorbid diseases contribute greatly to the mortality and morbidity of COPD (1,3). This disease may occur not only due to a decrease in lung compliance in adulthood, but also due to defects in lung development due to a number of risk factors in the intrauterine and early childhood period. Studies have suggested that COPD should be considered as a syndrome that affects all organs and systems rather than a single disease. Prevention of the disease is as important as its treatment (4).

The severity of the symptoms, the presence of emphysema, the frequency and severity of exacerbation, and the accompanying comorbid diseases determine the severity of COPD. The fact that it can vary from patient to patient, as well as showing different interactions in each attack, causes this disease to become heterogeneous and complex. The World Health Organization (WHO) accepts chronic bronchitis, emphysema, bronchiectasis, and asthma as part of the COPD definition (5). WHO data show that 3 million people die each year from this disease. Although the frequency of the disease increases with age, it is most common over the age of 40 and the prevalence of the disease in the world is 11.7% (6). In the data released by the Turkish Thoracic Society COPD Working Group, Turkey prevalence is 19.2%. Despite all the advances in the medical world, the definition, diagnostic criteria and treatment algorithms of the disease are still unclear due to the diversity and heterogeneity of the disease mechanism and phenotypic appearance

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Non-invasive mechanical ventilation or invasive mechanical ventilation may be required during intensive care follow-up. Respiratory acidosis ($\text{PaCO}_2 \geq 6.0$ kPa or 45mmHg and arterial $\text{pH} \leq 7.35$), use of assistive respiratory muscles, paradoxical breathing, intercostal withdrawal, dyspneic conditions showing increased respiratory load, and persistent hypoxemia despite supplemental oxygen are among the non-invasive mechanical ventilation indications. Invasive mechanical ventilation indications are; noninvasive ventilation, after cardiac arrest, unconsciousness and psychomotor agitation, massive aspiration and persistent vomiting, unstable cases despite fluid and vasoactive treatment can be listed as severe arrhythmias (1).

CONCLUSION

COPD is a life-threatening condition that is very common in today's conditions, causes frequent hospital admissions in both acute and chronic processes. It is an absolute condition to recognize COPD early and accurately, to apply the first intervention and treatment correctly, and to reduce the morbidity and mortality of patients. Therefore, it is an important responsibility for every physician to know and apply the correct approach to COPD in the presence of updated information. Following the latest studies in the literature is very important in order to manage the COPD process correctly.

REFERENCES

1. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. (2020 Report). https://goldcopd.org/wp-content/uploads/2019/12/ GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf (Last Access Date: 21.01.2021).
2. Miravittles M, Soler-Cataluña JJ, Calle M, et al. Spanish Guidelines for Management of Chronic Obstructive Pulmonary Disease (GesEPOC) 2017. Pharmacological Treatment of Stable Phase. *Arch Bronconeumol*, 2017;53(6):324-35.
3. Eisner MD, Anthonisen N, Coultas D. An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 2010;182:693.
4. Lopez AD, Mathers CD, Ezzati M, et al. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet*, 2006; 367: 1747- 57.
5. Bates CG. (2020). Chronic Obstructive Pulmonary Disease. Judith E Tintinalli. Tintinalli's Emergency Medicine A Comprehensive Study Guide 9 th Edition. (pp. 467-71). New York: McGraw-Hill Education.
6. Bhat TA, Panzica L, Kalathil SG, et al. Immune Dysfunction in Patients with Chronic Obstructive Pulmonary Disease. *Ann.Am Thorac Soc*, 2015; 12: 169-75.
7. Kocabaş A, Şen E, Bayram H et al. 2020. Identification, Epidemiology, Risk Factors, Diagnosis, Evaluation And Protective Approaches Report. Management of Chronic Obstructive Pulmonary Disease in Turkey: Prevention, Diagnosis and Treatment Standards Manual (pp.25). İstanbul: Institute of Public Health and Chronic Diseases.
8. Mirici A. 2019. Chronic Obstructive Pulmonary Disease. *Chest Diseases*(pp. 3-11). Respiratory Research Association of Turkey.

9. Zong DD, Ouyang RY, Chen P. Epigenetic mechanisms in chronic obstructive pulmonary disease. *Eur Rev Med Pharmacol Sci*, 2015; 19: 844-56.
10. Brusselle G, Bracke K. Targeting immune pathways for therapy in asthma and chronic obstructive pulmonary disease. *Ann Am Thorac Soc*, 2014; 11: 322-8.
11. National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease (acute exacerbation): antimicrobial prescribing 2018. <https://www.nice.org.uk/guidance/development/gidng10115/documents>. Accessed on 23.01.2021
12. Qaseem A, Wilt TJ, Weinberger SE, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann Intern Med*, 2011;155: 179.
13. Lamprecht B, Soriano JB, Studnicka M, et al: Determinants of underdiagnosis of COPD in national and international surveys. *Chest*, 2015; 148: 971.
14. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J*, 2005;26(5):948-68.
15. Gariani K, Delabavs A, Perneger TV, et al. Use of brain natriuretic peptide to detect previously unknown left ventricular dysfunction in patients with acute exacerbation of chronic obstructive pulmonary disease. *Swiss Med Wkly* 2011; 141: w13298.
16. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*, 2007; 356: 775.
17. Vogelmeier C, Kardos P, Harari S, et al. Formoterol mono- and combination therapy with tiotropium in patients with COPD: a 6-month study. *Respir Med*, 2001; 102: 1511.
18. Jones PW, Singh D, Bateman ED, et al. Efficacy and safety of twice-daily acclidinium bromide in COPD patients: the ATTAIN study. *Eur Respir J*, 2012; 40: 830.
19. Wood-Baker R, Walters J, Walters EH. Systemic corticosteroids in chronic obstructive pulmonary disease: an overview of Cochrane systematic reviews. *Respir Med*, 2007; 101: 371.
20. Han MK, Tayob N, Murray S. Predictors of chronic obstructive pulmonary disease exacerbation reduction in response to daily azithromycin therapy. *Am J Respir Crit Care Med*, 2014; 189: 1503.
21. Jolliffe DA, Greenberg L, Hooper RL, et al. Vitamin D to prevent exacerbations of COPD: systematic review and meta-analysis of individual participant data from randomised controlled trials. *Thorax*, January 2019;337-45.
22. Bardsley G, Pilcher J, McKinstry S, et al. Oxygen versus air-driven nebulisers for exacerbations of chronic obstructive pulmonary disease: a randomised controlled trial. *BMC Pulm Med*, 2018; 18: 157.

Chapter 3

THE MANAGEMENT OF PAINFUL BONE METASTASES

Mursel DUZOVA¹

INTRODUCTION

In accordance with the report announced by the World Health Organization (WHO) in September 2014, the number of cancer patients, which was 14 million in 2012, is estimated to reach 18 million in 2024 and 23 million in 2034 (1). As a result of advances in cancer treatment and care standards, the survival rates in these population have increased. Bone metastasis is the most common cause of chronic pain in cancer patients, and about 60% of patients with bone metastases feel serious pain (2). Bone is a structure that frequently metastasizes in cancer patients. It is the third greatest in amount common site of metastasis after lung and liver. Prostate and breast cancer (BC) are liable for the vast greater number (up to 70%) of bone metastases. This is due to both their high incidence and relatively long clinical course. The general amount of bone metastases are not fully known. Approximate amount of bone metastases according to tumor types with advanced metastatic disease: 70% in BC; 70% in prostate; 59% in thyroid; 35% in the lungs; 41% in the bladder; 20% in renal cell carcinoma and 14-45% in melanoma. Approximate life span from determination of bone metastasis: six months in melanoma; six months in the lungs; nine months in the bladder; twelve months in renal cell carcinoma; nearly 10-50 months in the prostate; nearly 20-24 months in BC, nearly 50 months in thyroid (3).

Bone Metastasis Development and Pain

The presence of high blood circulation in the bone tissue is a factor that facilitates the migration of metastatic cells. There are adhesion molecules on the surface of cancer cells that allow linking to bone marrow stromal cells and bone matrix. Besides, there are plenty of growth factors that support the establishment and proliferation of metastatic cells in the bone tissue. Bone tissue has intensive primary sensory afferent and sympathetic nerve innervation in the periosteum and intramedullary area (4).

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REFERENCES

1. Stewart BW, Wild CP. World Cancer Report 2014 (Print). Lyon Cedex: IARC Nonserial Publication; 2014
2. Mantyh P. The science behind metastatic bone pain. *Eur J Cancer* 2006;4(Suppl):4-8.
3. Macedo, F., Ladeira, K., Pinho, F., Saraiva, N., Bonito, N., Pinto, L., & Gonçalves, F. (2017). Bone metastases: an overview. *Oncology reviews*, 11(1).
4. Kingsley, L. A., Fournier, P. G., Chirgwin, J. M., & Guise, T. A. (2007). Molecular biology of bone metastasis. *Molecular cancer therapeutics*, 6(10), 2609-2617.
5. Zhu XC, Zhang JL, Ge CT, et al. Advances in cancer pain from bone metastasis. *Drug Des Devel Ther* 2015; 9: 4239-4245.
6. Basch E, Deal AM, Kris MG, et al. Symptom monitoring with patient-reported outcomes during routine cancer treatment: a randomized controlled trial. *J Clin Oncol* 2016;34:557-565.
7. Krajnik M, Zyllicz ZB. Pain Assessment, Recognising Clinical Patterns, and Cancer Pain Syndromes. In: Hanna M, Zyllicz ZB. editors. *Cancer Pain*. Springer London; 2013:95-108.
8. Mercadante S. Malignant bone pain: pathophysiology and treatment. *Pain* 1997;69:1-18.
9. Ahmad, I, Ahmed, MM, Ahsraf, MF, et al. pain management in metastatic bone disease: a literature review. *Cureus*. 2018;10:e3286.
10. Buga S, Sarria JE. The management of pain in metastatic bone disease. *Cancer Control* 2012;19:154-166.
11. Laird BJ, Walley J, Murray GD, Clausen E, Colvin LA, Fallon MT. Characterization of cancer-induced bone pain: an exploratory study. *Support Care Cancer* 2011; 19: 1393-401.
12. Rosenthal DI. Radiologic diagnosis of bone metastases. *Cancer* 1997;80:1595-607.
13. Ofluoglu O, Boriani S, Gasbarrini A, De Iure F, Donthineni R. Diagnosis and planning in the management of musculoskeletal tumors: surgical perspective. *Semin Intervent Radiol* 2010;27(2):185-90.
14. Qu X, Huang X, Yan W, Wu L, Dai K. A meta-analysis of (18)FDG-PET-CT, (18)FDG-PET, MRI and bone scintigraphy for diagnosis of bone metastases in patients with lung cancer. *Eur J Radiol* 2011; Epub 2011 Feb 25. doi:10.1016/j.ejrad.2011.01.126.
15. Erler K. Metastatik tümörlere ortopedik yaklaşım. *TOTBİD Dergisi* 2005;4(3-4):87-95.
16. Hipp JA, Springfield DS, Hayes WC. Predicting pathologic fracture risk in the management of metastatic bone defects. *Clin Orthop Relat Res* 1995;312:120-35.
17. Mirels H. Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathologic fractures. *Clin Orthop Relat Res* 1989;249:256-64.
18. Janjan NA. Radiation for bone metastases: conventional techniques and the role of systemic radiopharmaceuticals. *Cancer* 1997;80(8 Suppl):1628-45.
19. Chow, R., Hoskin, P., Schild, S. E., Raman, S., Im, J., Zhang, D., ... & Lock, M. (2019). Single vs multiple fraction palliative radiation therapy for bone metastases: cumulative meta-analysis. *Radiotherapy and Oncology*, 141, 56-61.
20. Bellido T, Plotkin LI. Novel actions of bisphosphonates in bone: preservation of osteoblast and osteocyte viability. *Bone* 2011;49(1):50-5.
21. Body JJ. Bisphosphonates for malignancy-related bone disease: current status, future developments. *Support Care Cancer* 2006;14(5):408-18.
22. Lutz S, Berk L, Chang E, Chow E, Hahn C, Hoskin P, Howell D, Konski A, Kachnic L, Lo S, Sahgal A, Silverman L, von Gunten C, Mendel E, Vassil A, Bruner DW, Hartsell W. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys* 2011;79(4):965-76.
23. van der Linden YM, Lok JJ, Steenland E, Martijn H, van Houwelingen H, Marijnen CAM, JWH Leer. Dutch Bone Metastasis Study Group. Single fraction radiotherapy is efficacious: a further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment. *Int J Radiat Oncol Biol Phys* 2004;59(2):528-37.
24. Palma DA, Salama JK, Lo SS, Senan S, Treasure T, Govindan R, Weichselbaum R. The oligometastatic state --separating truth from wishful thinking. *Nat Rev Clin Oncol* 2014;11(9):549-57.

25. De Felice F, Piccioli A, Musio D, Tombolini V. The role of radiation therapy in bone metastases management. *Oncotarget* 2017;8(15):25691–9.
26. Bhattacharya IS, Hoskin PJ. Stereotactic body radiotherapy for spinal and bone metastases. *Clin Oncol (R Coll Radiol)* 2015;27(5):298–306.
27. Ryu S, Deshmukh S, Timmerman RD, et al. Radiosurgery Compared To External Beam Radiotherapy for Localized Spine Metastasis: Phase III Results of NRG Oncology/RTOG 0631. *International Journal of Radiation Oncology • Biology • Physics*,105:S2-S3.
28. Bach, F, Larsen, B. H., Rohde, K., Børgesen, S. E., Gjerris, F., Bøge-Rasmussen, T., ... & Sørensen, P. S. (1990). Metastatic spinal cord compression. *Acta neurochirurgica*, 107(1), 37-43.
29. Laufer I, Rubin DG, Lis E, Cox BW, Stubblefield MD, Yamada Y, Bilsky MH. The NOMS framework: approach to the treatment of spinal metastatic tumors. *Oncologist* 2013;18(6):744–51.
30. Gomez DR, Tang C, Zhang J, et al. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. *J Clin Oncol* 2019;37:1558-1565.
31. McDonald R, Chow E, Rowbottom L, DeAngelis C, Soliman H. Incidence of pain flare in radiation treatment of bone metastases: A literature review. *J Bone Oncol* 2014;3:84-89.
32. Kato A, Minami K, Ito H, et al. Oxycodone-induced analgesic effects in a bone cancer pain model in mice. *Oncology* 2008;74(Suppl 1):55-60.
33. Smith HS, Mohsin I. Painful boney metastases. *Korean J Pain*. 2013;26:223-241.
34. Walker K, Medhurst SJ, Kidd BL, et al. Disease modifying and anti-nociceptive effects of the bisphosphonate zoledronic acid in a model of bone cancer pain. *Pain*. 2002;100:219-229.
35. Ripamonti CI, Santini D, Maranzano E, et al. Management of cancer pain: ESMO Clinical Practice Guidelines. *Ann Oncol* 2012;23(Suppl 7). vii139-54.
36. Fitzgibbon DR, Loeser JD. Spine and Bone Pain. In: *Cancer Pain: Assessment, Diagnosis, and Management*. Philadelphia, United States: Lippincott Williams & Wilkins; 2010. p. 303- 313.
37. Deer TR, Prager J, Levy R, et al. Polyanalgesic Consensus Conference 2012: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. *Neuromodulation* 2012;15:436-464.
38. Saliou G, Kocheida el M, Lehmann P, et al. Percutaneous vertebroplasty for pain management in malignant fractures of the spine with epidural involvement. *Radiology* 2010;254:882-890.
39. Qian Z, Sun Z, Yang H, et al. Kyphoplasty for the treatment of malignant vertebral compression fractures caused by metastases. *J Clin Neurosci* 2011;18:763-787.

Chapter 4

ACHALASIA, CURRENT UPDATE OF TREATMENT

Süleyman GÜNAY¹

INTRODUCTION

Achalasia is a disorder that affects the esophagus due to incomplete relaxation of the lower esophageal sphincter (LES). There has been no treatment option to achieve complete remission or cure for achalasia, and the aim is to relieve symptoms. Preventing the patient from severe esophageal dilatation is important because the treatment outcomes of the sigmoid or tortuous esophagus are poorer than the esophagus without severe dilatation (1). It seems that myotomy, whether endoscopic or surgical, is the definitive treatment of achalasia because of its durability and safety compared to other treatments. High-resolution manometry defines three types of achalasia which may be used to predict clinical success for each treatment option. EndoFlip provides hope for tailored treatment and a definitive diagnosis for achalasia which cannot be provided by high-resolution manometry. Furthermore, Peroral endoscopic myotomy started a new era for the treatment of achalasia without surgery. Therapy aims to ameliorate symptoms, provide gravitational esophagus emptying, preserve patients' nutrition and increase the quality of health.

Treatment Options

Currently, available treatment options include botulinum toxin injection (BTI), pneumatic dilatation (PD), laparoscopic Heller myotomy (LHM) with anti-reflux procedures, and POEM. Although other miscellaneous treatments like self-expandable metal stent placement, injection of ethanolamides to LES, or transcutaneous electrical nerve stimulation have been described, they are not recommended as standard therapies because of their low success rates or high complication rates in comparison to standard therapies (2-4). Esophagectomy should be the last option for patients who had failed in other therapies or had severely dilated esophagus. Treatment options are based on invasive procedures, whether endoscopic or surgical. Treatment protocols for each option show wide variations and may differ among centers. Treatments are driven by the physician's expertise or

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Author Contributions

S.G. searched the database with keywords, conducted the review of studies for each treatment option of achalasia, and decided which study will be used for the review. S.G wrote the article and prepared the tables. S.G. and S.G finally draft the article.

REFERENCES

1. Oude Nijhuis RAB, Prins LI, Mostafavi N, van Etten-Jamaludin FS, Smout A, Bredenoord AJ. Factors Associated With Achalasia Treatment Outcomes: Systematic Review and Meta-Analysis. *Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association.* 2020;18(7):1442-53.
2. Guelrud M, Rossiter A, Souney PF, Sulbaran M. Transcutaneous electrical nerve stimulation decreases lower esophageal sphincter pressure in patients with achalasia. *Digestive diseases and sciences.* 1991;36(8):1029-33. Epub 1991/08/01.
3. Mikaeli J, Veisari AK, Fazlollahi N, Mehrabi N, Soleimani HA, Shirani S, et al. Ethanolamine oleate versus botulinum toxin in the treatment of idiopathic achalasia. *Annals of gastroenterology.* 2015;28(2):229-35. Epub 2015/04/02.
4. Zhao JG, Li YD, Cheng YS, Li MH, Chen NW, Chen WX, et al. Long-term safety and outcome of a temporary self-expanding metallic stent for achalasia: a prospective study with a 13-year single-center experience. *European radiology.* 2009;19(8):1973-80. Epub 2009/03/20.
5. Field CE. Octyl nitrite in achalasia of the cardia. *Lancet* 1944;2:848-51.
6. Gelfond M, Rozen P, Keren S, Gilat T. Effect of nitrates on LOS pressure in achalasia: a potential therapeutic aid. *Gut.* 1981;22(4):312-8.
7. Traube M, Dubovik S, Lange RC, McCallum RW. The role of nifedipine therapy in achalasia: results of a randomized, double-blind, placebo-controlled study. *The American journal of gastroenterology.* 1989;84(10):1259-62.
8. Coccia G, Bortolotti M, Michetti P, Dodero M. Prospective clinical and manometric study comparing pneumatic dilatation and sublingual nifedipine in the treatment of oesophageal achalasia. *Gut.* 1991;32(6):604-6.
9. Arnon SS, Schechter R, Inglesby TV, Henderson DA, Bartlett JG, Ascher MS, et al. Botulinum toxin as a biological weapon: medical and public health management. *Jama.* 2001;285(8):1059-70.
10. Pasricha PJ, Ravich WJ, Hendrix TR, Sostre S, Jones B, Kalloo AN. Treatment of achalasia with intrasphincteric injection of botulinum toxin. A pilot trial. *Annals of internal medicine.* 1994;121(8):590-1.
11. Pasricha PJ, Ravich WJ, Hendrix TR, Sostre S, Jones B, Kalloo AN. Intrasphincteric botulinum toxin for the treatment of achalasia. *The New England journal of medicine.* 1995;332(12):774-8.
12. Campos GM, Vittinghoff E, Rabl C, Takata M, Gadenstatter M, Lin F, et al. Endoscopic and surgical treatments for achalasia: a systematic review and meta-analysis. *Annals of surgery.* 2009;249(1):45-57. Epub 2008/12/25.
13. Khashab MA, Vela MF, Thosani N, Agrawal D, Buxbaum JL, Abbas Fehmi SM, et al. ASGE guideline on the management of achalasia. *Gastrointestinal endoscopy.* 2020;91(2):213-27 e6.
14. van Hoeij FB, Tack JF, Pandolfino JE, Sternbach JM, Roman S, Smout AJ, et al. Complications of botulinum toxin injections for treatment of esophageal motility disordersdagger. *Diseases of the esophagus: official journal of the International Society for Diseases of the Esophagus.* 2017;30(3):1-5.
15. de Paiva A, Meunier FA, Molgo J, Aoki KR, Dolly JO. Functional repair of motor endplates after botulinum neurotoxin type A poisoning: biphasic switch of synaptic activity between nerve sprouts and their parent terminals. *Proceedings of the National Academy of Sciences of the*

- United States of America. 1999;96(6):3200-5.
16. Vaezi MF, Pandolfino JE, Yadlapati RH, Greer KB, Kavitt RT. ACG Clinical Guidelines: Diagnosis and Management of Achalasia. *The American journal of gastroenterology*. 2020;115(9):1393-411.
 17. Chuah SK, Lim CS, Liang CM, Lu HI, Wu KL, Changchien CS, et al. Bridging the Gap between Advancements in the Evolution of Diagnosis and Treatment towards Better Outcomes in Achalasia. *BioMed research international*. 2019;2019:8549187. Epub 2019/03/19.
 18. Vaezi MF, Pandolfino JE, Vela MF. ACG clinical guideline: diagnosis and management of achalasia. *The American journal of gastroenterology*. 2013;108(8):1238-49; quiz 50.
 19. Ghoshal UC, Kumar S, Saraswat VA, Aggarwal R, Misra A, Choudhuri G. Long-term follow-up after pneumatic dilation for achalasia cardia: factors associated with treatment failure and recurrence. *The American journal of gastroenterology*. 2004;99(12):2304-10.
 20. Howard JM, Mongan AM, Manning BJ, Byrne P, Lawler P, Ravi N, et al. Outcomes in achalasia from a surgical unit where pneumatic dilatation is first-line therapy. *Diseases of the esophagus: official journal of the International Society for Diseases of the Esophagus*. 2010;23(6):465-72.
 21. Cappell MS, Stavropoulos SN, Friedel D. Updated Systematic Review of Achalasia, with a Focus on POEM Therapy. *Digestive diseases and sciences*. 2020;65(1):38-65.
 22. Jia Y, Bustamante M, Moraveji S, McCallum RW. Pneumatic Dilation of the Lower Esophageal Sphincter Can Now Be Successfully Performed Without Morbidity. *The American journal of the medical sciences*. 2016;352(5):443-7.
 23. Allaix ME, Patti MG. Heller myotomy for achalasia. From the open to the laparoscopic approach. *World journal of surgery*. 2015;39(7):1603-7.
 24. Ellis FH, Jr. Oesophagomyotomy for achalasia: a 22-year experience. *The British journal of surgery*. 1993;80(7):882-5.
 25. Akuamoaa G. Achalasia oesophagi. Results of the Heller operation. *Acta chirurgica Scandinavica*. 1971;137(8):782-8.
 26. Pellegrini C, Wetter LA, Patti M, Leichter R, Mussan G, Mori T, et al. Thoracoscopic esophagomyotomy. Initial experience with a new approach for the treatment of achalasia. *Annals of surgery*. 1992;216(3):291-6; discussion 6-9.
 27. Andolfi C, Fisichella PM. Meta-analysis of clinical outcome after treatment for achalasia based on manometric subtypes. *The British journal of surgery*. 2019;106(4):332-41.
 28. Patti MG, Arcerito M, De Pinto M, Feo CV, Tong J, Gantert W, et al. Comparison of thoracoscopic and laparoscopic Heller myotomy for achalasia. *Journal of gastrointestinal surgery: official journal of the Society for Surgery of the Alimentary Tract*. 1998;2(6):561-6. Epub 1999/08/24.
 29. Douard R, Gaudric M, Chaussade S, Couturier D, Houssin D, Dousset B. Functional results after laparoscopic Heller myotomy for achalasia: A comparative study to open surgery. *Surgery*. 2004;136(1):16-24.
 30. Bonavina L, Nosadini A, Bardini R, Baessato M, Peracchia A. Primary treatment of esophageal achalasia. Long-term results of myotomy and Dor fundoplication. *Arch Surg*. 1992;127(2):222-6; discussion 7. Epub 1992/02/01.
 31. Siddaiah-Subramanya M, Yunus RM, Khan S, Memon B, Memon MA. Anterior Dor or Posterior Toupet with Heller Myotomy for Achalasia Cardia: A Systematic Review and Meta-Analysis. *World journal of surgery*. 2019;43(6):1563-70. Epub 2019/02/14.
 32. Barry L, Ross S, Dahal S, Morton C, Okpaleke C, Rosas M, et al. Laparoendoscopic single-site Heller myotomy with anterior fundoplication for achalasia. *Surgical endoscopy*. 2011;25(6):1766-74. Epub 2011/04/14.
 33. Melvin WS, Dundon JM, Talamini M, Horgan S. Computer-enhanced robotic telesurgery minimizes esophageal perforation during Heller myotomy. *Surgery*. 2005;138(4):553-8; discussion 8-9. Epub 2005/11/05.
 34. Ortega JA, Madureri V, Perez L. Endoscopic myotomy in the treatment of achalasia. *Gastrointestinal endoscopy*. 1980;26(1):8-10.

35. Inoue H, Minami H, Kobayashi Y, Sato Y, Kaga M, Suzuki M, et al. Peroral endoscopic myotomy (POEM) for esophageal achalasia. *Endoscopy*. 2010;42(4):265-71. Epub 2010/04/01.
36. Stavropoulos SN, Modayil RJ, Friedel D, Savides T. The International Per Oral Endoscopic Myotomy Survey (IPOEMS): a snapshot of the global POEM experience. *Surgical endoscopy*. 2013;27(9):3322-38.
37. Inoue H, Sato H, Ikeda H, Onimaru M, Sato C, Minami H, et al. Per-Oral Endoscopic Myotomy: A Series of 500 Patients. *Journal of the American College of Surgeons*. 2015;221(2):256-64.
38. Akintoye E, Kumar N, Obaitan I, Alayo QA, Thompson CC. Peroral endoscopic myotomy: a meta-analysis. *Endoscopy*. 2016;48(12):1059-68.
39. Crespin OM, Liu LWC, Parmar A, Jackson TD, Hamid J, Shlomovitz E, et al. Safety and efficacy of POEM for treatment of achalasia: a systematic review of the literature. *Surgical endoscopy*. 2017;31(5):2187-201. Epub 2016/09/17.
40. Patel K, Abbassi-Ghadi N, Markar S, Kumar S, Jethwa P, Zaninotto G. Peroral endoscopic myotomy for the treatment of esophageal achalasia: systematic review and pooled analysis. *Diseases of the esophagus: official journal of the International Society for Diseases of the Esophagus*. 2016;29(7):807-19. Epub 2015/07/16.
41. Evensen H, Kristensen V, Larssen L, Sandstad O, Hauge T, Medhus AW. Outcome of peroral endoscopic myotomy (POEM) in treatment-naive patients. A systematic review. *Scandinavian journal of gastroenterology*. 2019;54(1):1-7. Epub 2019/01/17.
42. Rohof WO, Salvador R, Annese V, Bruley des Varannes S, Chaussade S, Costantini M, et al. Outcomes of treatment for achalasia depend on manometric subtype. *Gastroenterology*. 2013;144(4):718-25; quiz e13-4. Epub 2013/01/02.
43. Kumbhari V, Tieu AH, Onimaru M, El Zein MH, Teitelbaum EN, Ujiki MB, et al. Peroral endoscopic myotomy (POEM) vs laparoscopic Heller myotomy (LHM) for the treatment of Type III achalasia in 75 patients: a multicenter comparative study. *Endoscopy international open*. 2015;3(3):E195-201. Epub 2015/07/15.
44. Werner YB, Hakanson B, Martinek J, Repici A, von Rahden BHA, Bredenoord AJ, et al. Endoscopic or Surgical Myotomy in Patients with Idiopathic Achalasia. *The New England journal of medicine*. 2019;381(23):2219-29. Epub 2019/12/05.
45. Nabi Z, Reddy DN, Ramchandani M. Adverse events during and after per-oral endoscopic myotomy: prevention, diagnosis, and management. *Gastrointestinal endoscopy*. 2018;87(1):4-17.
46. Cai MY, Zhou PH, Yao LQ, Zhu BQ, Liang L, Li QL. Thoracic CT after peroral endoscopic myotomy for the treatment of achalasia. *Gastrointestinal endoscopy*. 2014;80(6):1046-55.
47. Pannu D, Yang D, Abbitt PL, Draganov PV. Prospective evaluation of CT esophagram findings after peroral endoscopic myotomy. *Gastrointestinal endoscopy*. 2016;84(3):408-15.
48. Haito-Chavez Y, Inoue H, Beard KW, Draganov PV, Ujiki M, Rahden BHA, et al. Comprehensive Analysis of Adverse Events Associated With Per Oral Endoscopic Myotomy in 1826 Patients: An International Multicenter Study. *The American journal of gastroenterology*. 2017;112(8):1267-76.
49. Wang Y, Liu ZQ, Xu MD, Chen SY, Zhong YS, Zhang YQ, et al. Clinical and endoscopic predictors for intraprocedural mucosal injury during per-oral endoscopic myotomy. *Gastrointestinal endoscopy*. 2019;89(4):769-78.
50. Kumbhari V, Azola A, Saxena P, Modayil R, Kalloo AN, Stavropoulos SN, et al. Closure methods in submucosal endoscopy. *Gastrointestinal endoscopy*. 2014;80(5):894-5.
51. Pescarus R, Shlomovitz E, Sharata AM, Cassera MA, Reavis KM, Dunst CM, et al. Endoscopic suturing versus endoscopic clip closure of the mucosotomy during a per-oral endoscopic myotomy (POEM): a case-control study. *Surgical endoscopy*. 2016;30(5):2132-5.
52. Werner YB, von Renteln D, Noder T, Schachschal G, Denzer UW, Groth S, et al. Early adverse events of per-oral endoscopic myotomy. *Gastrointestinal endoscopy*. 2017;85(4):708-18 e2.
53. Misra L, Fukami N, Nikolic K, Trentman TL. Peroral endoscopic myotomy: procedural complications and pain management for the perioperative clinician. *Medical devices*. 2017;10:53-9.
54. Mundre P, Black CJ, Mohammed N, Ford AC. Efficacy of surgical or endoscopic treatment of

- idiopathic achalasia: a systematic review and network meta-analysis. *The lancet Gastroenterology & hepatology*. 2020.
55. Teitelbaum EN, Boris L, Arafat FO, Nicodeme F, Lin Z, Kahrilas PJ, et al. Comparison of esophago-gastric junction distensibility changes during POEM and Heller myotomy using intraoperative FLIP. *Surgical endoscopy*. 2013;27(12):4547-55.
 56. Teitelbaum EN, Soper NJ, Pandolfino JE, Kahrilas PJ, Hirano I, Boris L, et al. Esophago-gastric junction distensibility measurements during Heller myotomy and POEM for achalasia predict postoperative symptomatic outcomes. *Surgical endoscopy*. 2015;29(3):522-8.
 57. Duranceau A, Liberman M, Martin J, Ferraro P. End-stage achalasia. *Diseases of the esophagus: official journal of the International Society for Diseases of the Esophagus*. 2012;25(4):319-30.
 58. Vela MF, Richter JE, Wachsberger D, Connor J, Rice TW. Complexities of managing achalasia at a tertiary referral center: use of pneumatic dilatation, Heller myotomy, and botulinum toxin injection. *The American journal of gastroenterology*. 2004;99(6):1029-36.
 59. Miller DL, Allen MS, Trastek VF, Deschamps C, Pairolero PC. Esophageal resection for recurrent achalasia. *The Annals of thoracic surgery*. 1995;60(4):922-5; discussion 5-6.
 60. Aiolfi A, Asti E, Bonitta G, Bonavina L. Esophagectomy for End-Stage Achalasia: Systematic Review and Meta-analysis. *World journal of surgery*. 2018;42(5):1469-76.
 61. Moonen A, Annese V, Belmans A, Bredenoord AJ, Bruley des Varannes S, Costantini M, et al. Long-term results of the European achalasia trial: a multicentre randomized controlled trial comparing pneumatic dilation versus laparoscopic Heller myotomy. *Gut*. 2016;65(5):732-9. Epub 2015/11/29.
 62. Boeckxstaens GE, Annese V, des Varannes SB, Chaussade S, Costantini M, Cuttitta A, et al. Pneumatic dilation versus laparoscopic Heller's myotomy for idiopathic achalasia. *The New England journal of medicine*. 2011;364(19):1807-16. Epub 2011/05/13.
 63. Kumbhari V, Behary J, Szczesniak M, Zhang T, Cook IJ. Efficacy and safety of pneumatic dilatation for achalasia in the treatment of post-myotomy symptom relapse. *The American journal of gastroenterology*. 2013;108(7):1076-81. Epub 2013/03/06.
 64. Borges AA, Lemme EM, Abrahao LJ, Jr., Madureira D, Andrade MS, Soldan M, et al. Pneumatic dilation versus laparoscopic Heller myotomy for the treatment of achalasia: variables related to a good response. *Diseases of the esophagus: official journal of the International Society for Diseases of the Esophagus*. 2014;27(1):18-23. Epub 2013/04/05.
 65. Swanstrom LL. POEM outcomes: How long is long enough? *Gastrointestinal endoscopy*. 2017;85(5):934-5.
 66. Teitelbaum EN, Dunst CM, Reavis KM, Sharata AM, Ward MA, DeMeester SR, et al. Clinical outcomes five years after POEM for treatment of primary esophageal motility disorders. *Surgical endoscopy*. 2018;32(1):421-7.
 67. Annese V, Basciani M, Lombardi G, Caruso N, Perri F, Simone P, et al. Perendoscopic injection of botulinum toxin is effective in achalasia after failure of myotomy or pneumatic dilation. *Gastrointestinal endoscopy*. 1996;44(4):461-5.
 68. Mikaeli J, Bishehsari F, Motazeri G, Mahdavinia M, Yaghoobi M, Darvish-Moghadam S, et al. Injection of botulinum toxin before pneumatic dilatation in achalasia treatment: a randomized-controlled trial. *Alimentary pharmacology & therapeutics*. 2006;24(6):983-9.
 69. Smith CD, Stival A, Howell DL, Swafford V. Endoscopic therapy for achalasia before Heller myotomy results in worse outcomes than heller myotomy alone. *Annals of surgery*. 2006;243(5):579-84; discussion 84-6.
 70. Carter JT, Nguyen D, Roll GR, Ma SW, Way LW. Predictors of long-term outcome after laparoscopic esophagomyotomy and Dor fundoplication for achalasia. *Archives of surgery*. 2011;146(9):1024-8.
 71. Yeniova AO, Yoo IK, Jeong E, Cho JY. Comparison of peroral endoscopic myotomy between de-novo achalasia and achalasia with prior treatment. *Surgical endoscopy*. 2020.
 72. Amani M, Fazlollahi N, Shirani S, Malekzadeh R, Mikaeli J. Assessment of pneumatic balloon dilation in patients with symptomatic relapse after failed Heller myotomy: a single center experience.

- rience. *Middle East J Dig Dis.* 2016;8.
73. Kumbhari V, Behary J, Szczesniak M, Zhang T, Cook IJ. Efficacy and safety of pneumatic dilatation for achalasia in the treatment of post-myotomy symptom relapse. *The American journal of gastroenterology.* 2013;108.
 74. Legros L, Ropert A, Brochard C, Bouguen G, Pagenault M, Siproudhis L, et al. Long-term results of pneumatic dilatation for relapsing symptoms of achalasia after Heller myotomy. *Neurogastroenterol Motil.* 2014;26(9):1248-55.
 75. Fernandez-Ananin S, Fernandez AF, Balague C, Sacoto D, Targarona EM. What to do when Heller's myotomy fails? Pneumatic dilatation, laparoscopic remyotomy or peroral endoscopic myotomy: A systematic review. *Journal of minimal access surgery.* 2018;14(3):177-84.
 76. Ichkhanian Y, Assis D, Familiari P, Ujiki MB, Su B, Khan SR, et al. Management of Patients after Failed Peroral Endoscopic Myotomy: a Multicenter Study. *Endoscopy.* 2020. Epub 2020/11/17.
 77. Morino M, Rebecchi F, Festa V, Garrone C. Preoperative pneumatic dilatation represents a risk factor for laparoscopic Heller myotomy. *Surgical endoscopy.* 1997;11(4):359-61.
 78. Veenstra BR, Goldberg RF, Bowers SP, Thomas M, Hinder RA, Smith CD. Revisional surgery after failed esophagogastric myotomy for achalasia: successful esophageal preservation. *Surgical endoscopy.* 2016;30(5):1754-61. Epub 2015/08/16.
 79. Ngamruengphong S, Inoue H, Ujiki MB, Patel LY, Bapaye A, Desai PN, et al. Efficacy and Safety of Peroral Endoscopic Myotomy for Treatment of Achalasia After Failed Heller Myotomy. *Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association.* 2017;15(10):1531-7 e3.
 80. Tan S, Zhong C, Ren Y, Luo X, Xu J, Fu X, et al. Efficacy and Safety of Peroral Endoscopic Myotomy in Achalasia Patients with Failed Previous Intervention: A Systematic Review and Meta-Analysis. *Gut and liver.* 2020.
 81. Ling T, Guo H, Zou X. Effect of peroral endoscopic myotomy in achalasia patients with failure of prior pneumatic dilation: a prospective case-control study. *Journal of gastroenterology and hepatology.* 2014;29(8):1609-13. Epub 2014/03/19.
 82. Sharata A, Kurian AA, Dunst CM, Bhayani NH, Reavis KM, Swanstrom LL. Peroral endoscopic myotomy (POEM) is safe and effective in the setting of prior endoscopic intervention. *Journal of gastrointestinal surgery: official journal of the Society for Surgery of the Alimentary Tract.* 2013;17(7):1188-92. Epub 2013/04/24.
 83. Orenstein SB, Raigani S, Wu YV, Pauli EM, Phillips MS, Ponsky JL, et al. Peroral endoscopic myotomy (POEM) leads to similar results in patients with and without prior endoscopic or surgical therapy. *Surgical endoscopy.* 2015;29(5):1064-70. Epub 2014/09/25.
 84. Jones EL, Meara MP, Pittman MR, Hazey JW, Perry KA. Prior treatment does not influence the performance or early outcome of per-oral endoscopic myotomy for achalasia. *Surgical endoscopy.* 2016;30(4):1282-6. Epub 2015/07/01.
 85. Tang X, Gong W, Deng Z, Zhou J, Ren Y, Zhang Q, et al. Feasibility and safety of peroral endoscopic myotomy for achalasia after failed endoscopic interventions. *Diseases of the esophagus: official journal of the International Society for Diseases of the Esophagus.* 2017;30(3):1-6. Epub 2016/11/24.
 86. Nabi Z, Ramchandani M, Chavan R, Tandan M, Kalapala R, Darisetty S, et al. Peroral endoscopic myotomy in treatment-naïve achalasia patients versus prior treatment failure cases. *Endoscopy.* 2018;50(4):358-70. Epub 2017/11/24.
 87. Liu ZQ, Li QL, Chen WF, Zhang XC, Wu QN, Cai MY, et al. The effect of prior treatment on clinical outcomes in patients with achalasia undergoing peroral endoscopic myotomy. *Endoscopy.* 2019;51(4):307-16. Epub 2018/09/28.
 88. Annese V, Basciani M, Perri F, Lombardi G, Frusciante V, Simone P, et al. Controlled trial of botulinum toxin injection versus placebo and pneumatic dilation in achalasia. *Gastroenterology.* 1996;111(6):1418-24. Epub 1996/12/01.
 89. Vaezi MF, Richter JE, Wilcox CM, Schroeder PL, Birgisson S, Slaughter RL, et al. Botulinum toxin versus pneumatic dilatation in the treatment of achalasia: a randomized trial. *Gut.*

- 1999;44(2):231-9.
90. Muehldorfer SM, Schneider TH, Hochberger J, Martus P, Hahn EG, Ell C. Esophageal achalasia: intrasphincteric injection of botulinum toxin A versus balloon dilation. *Endoscopy*. 1999;31(7):517-21.
 91. Ghoshal UC, Chaudhuri S, Pal BB, Dhar K, Ray G, Banerjee PK. Randomized controlled trial of intrasphincteric botulinum toxin A injection versus balloon dilatation in treatment of achalasia cardia. *Diseases of the esophagus: official journal of the International Society for Diseases of the Esophagus*. 2001;14(3-4):227-31.
 92. Bansal R, Nostrant TT, Scheiman JM, Koshy S, Barnett JL, Elta GH, et al. Intrasphincteric botulinum toxin versus pneumatic balloon dilation for treatment of primary achalasia. *Journal of clinical gastroenterology*. 2003;36(3):209-14.
 93. Mikaeli J, Fazel A, Montazeri G, Yaghoobi M, Malekzadeh R. Randomized controlled trial comparing botulinum toxin injection to pneumatic dilatation for the treatment of achalasia. *Alimentary pharmacology & therapeutics*. 2001;15(9):1389-96.
 94. Zhu Q, Liu J, Yang C. Clinical study on combined therapy of botulinum toxin injection and small balloon dilation in patients with esophageal achalasia. *Digestive surgery*. 2009;26(6):493-8.
 95. Bakhshipour A, Rabbani R, Shirani S, Soleimani HA, Mikaeli J. Comparison of pneumatic dilation with pneumatic dilation plus botulinum toxin for treatment of achalasia. *Acta medica Iranica*. 2010;48(2):107-10.
 96. Allescher HD, Storr M, Seige M, Gonzales-Donoso R, Ott R, Born P, et al. Treatment of achalasia: botulinum toxin injection vs. pneumatic balloon dilation. A prospective study with long-term follow-Up. *Endoscopy*. 2001;33(12):1007-17. Epub 2001/12/12.
 97. Leyden JE, Moss AC, MacMathuna P. Endoscopic pneumatic dilation versus botulinum toxin injection in the management of primary achalasia. *The Cochrane database of systematic reviews*. 2014(12):CD005046. Epub 2014/12/09.
 98. Andrews CN, Anvari M, Dobranowski J. Laparoscopic Heller's myotomy or botulinum toxin injection for management of esophageal achalasia. Patient choice and treatment outcomes. *Surgical endoscopy*. 1999;13(8):742-6. Epub 1999/08/03.
 99. Zaninotto G, Annese V, Costantini M, Del Genio A, Costantino M, Epifani M, et al. Randomized controlled trial of botulinum toxin versus laparoscopic heller myotomy for esophageal achalasia. *Annals of surgery*. 2004;239(3):364-70. Epub 2004/04/13.
 100. Kostic S, Kjellin A, Ruth M, Lonroth H, Johnsson E, Andersson M, et al. Pneumatic dilatation or laparoscopic cardiomyotomy in the management of newly diagnosed idiopathic achalasia. Results of a randomized controlled trial. *World journal of surgery*. 2007;31(3):470-8. Epub 2007/02/20.
 101. Persson J, Johnsson E, Kostic S, Lundell L, Smedh U. Treatment of achalasia with laparoscopic myotomy or pneumatic dilatation: long-term results of a prospective, randomized study. *World journal of surgery*. 2015;39(3):713-20. Epub 2014/11/21.
 102. Suarez J, Mearin F, Boque R, Zanon V, Armengol JR, Pradell J, et al. Laparoscopic myotomy vs endoscopic dilation in the treatment of achalasia. *Surgical endoscopy*. 2002;16(1):75-7. Epub 2002/04/19.
 103. Novais PA, Lemme EM. 24-h pH monitoring patterns and clinical response after achalasia treatment with pneumatic dilation or laparoscopic Heller myotomy. *Alimentary pharmacology & therapeutics*. 2010;32(10):1257-65. Epub 2010/10/20.
 104. Tabola R, Grabowski K, Lewandowski A, Augoff K, Markocka-Maczka K. Achalasia--balloon dilation or surgery? *Medical science monitor: international medical journal of experimental and clinical research*. 2013;19:1089-94. Epub 2013/12/04.
 105. Wang HM, Tai WC, Chuah SK, Lu HI, Lu LS, Liang CM, et al. Comparison of treatment outcomes of endoscope-guided pneumatic dilation and laparoscopic Heller myotomy. *The Kaohsiung journal of medical sciences*. 2015;31(12):639-43. Epub 2015/12/29.
 106. Hamdy E, El Nakeeb A, El Hanfy E, El Hemaly M, Salah T, Hamed H, et al. Comparative Study Between Laparoscopic Heller Myotomy Versus Pneumatic Dilatation for Treatment of Early

- Achalasia: A Prospective Randomized Study. *Journal of laparoendoscopic & advanced surgical techniques Part A*. 2015;25(6):460-4. Epub 2015/05/08.
107. Chrystoja CC, Darling GE, Diamant NE, Kortan PP, Tomlinson GA, Deitel W, et al. Achalasia-Specific Quality of Life After Pneumatic Dilation or Laparoscopic Heller Myotomy With Partial Fundoplication: A Multicenter, Randomized Clinical Trial. *The American journal of gastroenterology*. 2016;111(11):1536-45. Epub 2016/11/04.
 108. Vela MF, Richter JE, Khandwala F, Blackstone EH, Wachsberger D, Baker ME, et al. The long-term efficacy of pneumatic dilatation and Heller myotomy for the treatment of achalasia. *Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association*. 2006;4(5):580-7. Epub 2006/04/25.
 109. Harvey PR, Coupland B, Mytton J, Evison F, Patel P, Trudgill NJ. Outcomes of pneumatic dilatation and Heller's myotomy for achalasia in England between 2005 and 2016. *Gut*. 2019;68(7):1146-51. Epub 2019/01/05.
 110. Karanicolas PJ, Smith SE, Inculet RI, Malthaner RA, Reynolds RP, Goeree R, et al. The cost of laparoscopic myotomy versus pneumatic dilatation for esophageal achalasia. *Surgical endoscopy*. 2007;21(7):1198-206. Epub 2007/05/05.
 111. Gray RT, Coleman HG, Lau KW, McCaughey C, Coyle PV, Murray LJ, et al. Heller's myotomy and pneumatic dilatation in the treatment of achalasia: a population-based case-control study assessing long-term quality of life. *Diseases of the esophagus: official journal of the International Society for Diseases of the Esophagus*. 2017;30(3):1-7. Epub 2015/11/07.
 112. Csendes A, Velasco N, Braghetto I, Henriquez A. A prospective randomized study comparing forceful dilatation and esophagomyotomy in patients with achalasia of the esophagus. *Gastroenterology*. 1981;80(4):789-95. Epub 1981/04/01.
 113. Csendes A, Braghetto I, Henriquez A, Cortes C. Late results of a prospective randomized study comparing forceful dilatation and oesophagomyotomy in patients with achalasia. *Gut*. 1989;30(3):299-304. Epub 1989/03/01.
 114. Cheng JW, Li Y, Xing WQ, Lv HW, Wang HR. Laparoscopic Heller myotomy is not superior to pneumatic dilation in the management of primary achalasia: Conclusions of a systematic review and meta-analysis of randomized controlled trials. *Medicine*. 2017;96(7):e5525. Epub 2017/02/17.
 115. Illes A, Farkas N, Hegyi P, Garami A, Szabo I, Solymar M, et al. Is Heller myotomy better than balloon dilation? A meta-analysis. *Journal of gastrointestinal and liver diseases: JGLD*. 2017;26(2):121-7. Epub 2017/06/16.
 116. Baniya R, Upadhaya S, Khan J, Subedi SK, Shaik Mohammed T, Ganatra BK, et al. Laparoscopic esophageal myotomy versus pneumatic dilation in the treatment of idiopathic achalasia: a meta-analysis of randomized controlled trials. *Clinical and experimental gastroenterology*. 2017;10:241-8. Epub 2017/10/14.
 117. Bonifacio P, de Moura DTH, Bernardo WM, de Moura ETH, Farias GFA, Neto ACM, et al. Pneumatic dilation versus laparoscopic Heller's myotomy in the treatment of achalasia: systematic review and meta-analysis based on randomized controlled trials. *Diseases of the esophagus: official journal of the International Society for Diseases of the Esophagus*. 2019;32(2). Epub 2018/11/01.
 118. Yaghoobi M, Mayrand S, Martel M, Roshan-Afshar I, Bijarchi R, Barkun A. Laparoscopic Heller's myotomy versus pneumatic dilation in the treatment of idiopathic achalasia: a meta-analysis of randomized, controlled trials. *Gastrointestinal endoscopy*. 2013;78(3):468-75. Epub 2013/05/21.
 119. Schoenberg MB, Marx S, Kersten JF, Rosch T, Belle S, Kahler G, et al. Laparoscopic Heller myotomy versus endoscopic balloon dilatation for the treatment of achalasia: a network meta-analysis. *Annals of surgery*. 2013;258(6):943-52. Epub 2013/11/14.
 120. Wang L, Li YM, Li L. Meta-analysis of randomized and controlled treatment trials for achalasia. *Digestive diseases and sciences*. 2009;54(11):2303-11. Epub 2008/12/25.

121. de Heer J, Desai M, Boeckxstaens G, Zaninotto G, Fuchs KH, Sharma P, et al. Pneumatic balloon dilatation versus laparoscopic Heller myotomy for achalasia: a failed attempt at meta-analysis. *Surgical endoscopy*. 2020. Epub 2020/03/18.
122. Wang X, Tan Y, Lv L, Zhu H, Chu Y, Li C, et al. Peroral endoscopic myotomy versus pneumatic dilation for achalasia in patients aged ≥ 65 years. *Revista espanola de enfermedades digestivas : organo oficial de la Sociedad Espanola de Patologia Digestiva*. 2016;108(10):637-41. Epub 2016/09/22.
123. Meng F, Li P, Wang Y, Ji M, Wu Y, Yu L, et al. Peroral endoscopic myotomy compared with pneumatic dilation for newly diagnosed achalasia. *Surgical endoscopy*. 2017;31(11):4665-72. Epub 2017/04/16.
124. Ponds FA, Fockens P, Lei A, Neuhaus H, Beyna T, Kandler J, et al. Effect of Peroral Endoscopic Myotomy vs Pneumatic Dilation on Symptom Severity and Treatment Outcomes Among Treatment-Naive Patients With Achalasia: A Randomized Clinical Trial. *Jama*. 2019;322(2):134-44. Epub 2019/07/10.
125. Yadlapati R, Gupta S. Peroral Endoscopic Myotomy versus Pneumatic Dilation in Achalasia: Dissecting the Randomized Controlled Trial. *Gastroenterology*. 2020;158(1):276-7. Epub 2019/11/11.
126. Zhong C, Tan S, Huang S, Lu M, Peng Y, Fu X, et al. Peroral endoscopic myotomy versus pneumatic dilation for achalasia: a systematic review and meta-analysis. *European journal of gastroenterology & hepatology*. 2020;32(11):1413-21.
127. Ramirez M, Zubieta C, Ciotola F, Amenabar A, Badaloni A, Nachman F, et al. Per oral endoscopic myotomy vs. laparoscopic Heller myotomy, does gastric extension length matter? *Surgical endoscopy*. 2018;32(1):282-8.
128. Hanna AN, Datta J, Ginzberg S, Dasher K, Ginsberg GG, Dempsey DT. Laparoscopic Heller Myotomy vs Per Oral Endoscopic Myotomy: Patient-Reported Outcomes at a Single Institution. *Journal of the American College of Surgeons*. 2018;226(4):465-72 e1.
129. Peng L, Tian S, Du C, Yuan Z, Guo M, Lu L. Outcome of Peroral Endoscopic Myotomy (POEM) for Treating Achalasia Compared With Laparoscopic Heller Myotomy (LHM). *Surgical laparoscopy, endoscopy & percutaneous techniques*. 2017;27(1):60-4.
130. Leeds SG, Burdick JS, Ogola GO, Ontiveros E. Comparison of outcomes of laparoscopic Heller myotomy versus per-oral endoscopic myotomy for management of achalasia. *Proceedings*. 2017;30(4):419-23.
131. Khashab MA, Kumbhari V, Tieu AH, El Zein MH, Ismail A, Ngamruengphong S, et al. Peroral endoscopic myotomy achieves similar clinical response but incurs lesser charges compared to robotic heller myotomy. *Saudi journal of gastroenterology: official journal of the Saudi Gastroenterology Association*. 2017;23(2):91-6.
132. de Pascale S, Repici A, Puccetti F, Cariani E, Rosati R, Fumagalli U. Peroral endoscopic myotomy versus surgical myotomy for primary achalasia: single-center, retrospective analysis of 74 patients. *Diseases of the esophagus: official journal of the International Society for Diseases of the Esophagus*. 2017;30(8):1-7.
133. Schneider AM, Louie BE, Warren HF, Farivar AS, Schembre DB, Aye RW. A Matched Comparison of Per Oral Endoscopic Myotomy to Laparoscopic Heller Myotomy in the Treatment of Achalasia. *Journal of gastrointestinal surgery: official journal of the Society for Surgery of the Alimentary Tract*. 2016;20(11):1789-96.
134. Sanaka MR, Hayat U, Thota PN, Jegadeesan R, Ray M, Gabbard SL, et al. Efficacy of peroral endoscopic myotomy vs other achalasia treatments in improving esophageal function. *World journal of gastroenterology*. 2016;22(20):4918-25.
135. Teitelbaum EN, Rajeswaran S, Zhang R, Sieberg RT, Miller FH, Soper NJ, et al. Peroral esophageal myotomy (POEM) and laparoscopic Heller myotomy produce a similar short-term anatomic and functional effect. *Surgery*. 2013;154(4):885-91; discussion 91-2.
136. Vigneswaran Y, Yetasook AK, Zhao JC, Denham W, Linn JG, Ujiki MB. Peroral endoscopic myotomy (POEM): feasible as reoperation following Heller myotomy. *Journal of gastrointesti-*

- nal surgery: official journal of the Society for Surgery of the Alimentary Tract. 2014;18(6):1071-6.
137. Hungness ES, Teitelbaum EN, Santos BF, Arafat FO, Pandolfino JE, Kahrilas PJ, et al. Comparison of perioperative outcomes between peroral esophageal myotomy (POEM) and laparoscopic Heller myotomy. *Journal of gastrointestinal surgery: official journal of the Society for Surgery of the Alimentary Tract.* 2013;17(2):228-35.
 138. Bhayani NH, Kurian AA, Dunst CM, Sharata AM, Rieder E, Swanstrom LL. A comparative study on comprehensive, objective outcomes of laparoscopic Heller myotomy with per-oral endoscopic myotomy (POEM) for achalasia. *Annals of surgery.* 2014;259(6):1098-103.
 139. Ujiki MB, Yetasook AK, Zapf M, Linn JG, Carbray JM, Denham W. Peroral endoscopic myotomy: A short-term comparison with the standard laparoscopic approach. *Surgery.* 2013;154(4):893-7; discussion 7-900.
 140. Docimo S, Jr., Mathew A, Shope AJ, Winder JS, Haluck RS, Pauli EM. Reduced postoperative pain scores and narcotic use favor per-oral endoscopic myotomy over laparoscopic Heller myotomy. *Surgical endoscopy.* 2017;31(2):795-800.
 141. Kumbhari V, Familiari P, Bjerregaard NC, Pioche M, Jones E, Ko WJ, et al. Gastroesophageal reflux after peroral endoscopic myotomy: a multicenter case-control study. *Endoscopy.* 2017;49(7):634-42.
 142. Repici A, Fuccio L, Maselli R, Mazza F, Correale L, Mandolesi D, et al. GERD after per-oral endoscopic myotomy as compared with Heller's myotomy with fundoplication: a systematic review with meta-analysis. *Gastrointestinal endoscopy.* 2018;87(4):934-43 e18.
 143. Schlottmann F, Luckett DJ, Fine J, Shaheen NJ, Patti MG. Laparoscopic Heller Myotomy Versus Peroral Endoscopic Myotomy (POEM) for Achalasia: A Systematic Review and Meta-analysis. *Annals of surgery.* 2018;267(3):451-60.
 144. Marano L, Pallabazzer G, Solito B, Santi S, Pigazzi A, De Luca R, et al. Surgery or Peroral Esophageal Myotomy for Achalasia: A Systematic Review and Meta-Analysis. *Medicine.* 2016;95(10):e3001.
 145. Zhang Y, Wang H, Chen X, Liu L, Wang H, Liu B, et al. Per-Oral Endoscopic Myotomy Versus Laparoscopic Heller Myotomy for Achalasia: A Meta-Analysis of Nonrandomized Comparative Studies. *Medicine.* 2016;95(6):e2736.
 146. Talukdar R, Inoue H, Nageshwar Reddy D. Efficacy of peroral endoscopic myotomy (POEM) in the treatment of achalasia: a systematic review and meta-analysis. *Surgical endoscopy.* 2015;29(11):3030-46.
 147. Awaiz A, Yunus RM, Khan S, Memon B, Memon MA. Systematic Review and Meta-Analysis of Perioperative Outcomes of Peroral Endoscopic Myotomy (POEM) and Laparoscopic Heller Myotomy (LHM) for Achalasia. *Surgical laparoscopy, endoscopy & percutaneous techniques.* 2017;27(3):123-31.
 148. Martins RK, Ribeiro IB, DTH DEM, Hathorn KE, Bernardo WM, EGH DEM. Peroral (Poem) or Surgical Myotomy for the Treatment of Achalasia: A Systematic Review and Meta-Analysis. *Arquivos de gastroenterologia.* 2020;57(1):79-86.
 149. Park CH, Jung DH, Kim DH, Lim CH, Moon HS, Park JH, et al. Comparative efficacy of per-oral endoscopic myotomy and Heller myotomy in patients with achalasia: a meta-analysis. *Gastrointestinal endoscopy.* 2019;90(4):546-58 e3.
 150. Mundre P, Black CJ, Mohammed N, Ford AC. Efficacy of surgical or endoscopic treatment of idiopathic achalasia: a systematic review and network meta-analysis. *The lancet Gastroenterology & hepatology.* 2021;6(1):30-8.
 151. Aiolfi A, Bona D, Riva CG, Micheletto G, Rausa E, Campanelli G, et al. Systematic Review and Bayesian Network Meta-Analysis Comparing Laparoscopic Heller Myotomy, Pneumatic Dilatation, and Peroral Endoscopic Myotomy for Esophageal Achalasia. *Journal of laparoendoscopic & advanced surgical techniques Part A.* 2020;30(2):147-55. *copy.* 2019;51(4):307-16. Epub 2018/09/28.
 132. Annese V, Basciani M, Perri F, Lombardi G, Frusciante V, Simone P, et al. Controlled trial of bo-

- tulinum toxin injection versus placebo and pneumatic dilation in achalasia. *Gastroenterology*. 1996;111(6):1418-24. Epub 1996/12/01.
133. Vaezi MF, Richter JE, Wilcox CM, Schroeder PL, Birgisson S, Slaughter RL, et al. Botulinum toxin versus pneumatic dilatation in the treatment of achalasia: a randomised trial. *Gut*. 1999;44(2):231-9.
134. Muehldorfer SM, Schneider TH, Hochberger J, Martus P, Hahn EG, Ell C. Esophageal achalasia: intrasphincteric injection of botulinum toxin A versus balloon dilation. *Endoscopy*. 1999;31(7):517-21.
135. Ghoshal UC, Chaudhuri S, Pal BB, Dhar K, Ray G, Banerjee PK. Randomized controlled trial of intrasphincteric botulinum toxin A injection versus balloon dilatation in treatment of achalasia cardia. *Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus*. 2001;14(3-4):227-31.
136. Bansal R, Nostrant TT, Scheiman JM, Koshy S, Barnett JL, Elta GH, et al. Intrasphincteric botulinum toxin versus pneumatic balloon dilation for treatment of primary achalasia. *Journal of clinical gastroenterology*. 2003;36(3):209-14.
137. Mikaeli J, Fazel A, Montazeri G, Yaghoobi M, Malekzadeh R. Randomized controlled trial comparing botulinum toxin injection to pneumatic dilatation for the treatment of achalasia. *Alimentary pharmacology & therapeutics*. 2001;15(9):1389-96.
138. Zhu Q, Liu J, Yang C. Clinical study on combined therapy of botulinum toxin injection and small balloon dilation in patients with esophageal achalasia. *Digestive surgery*. 2009;26(6):493-8.
139. Bakhshipour A, Rabbani R, Shirani S, Soleimani HA, Mikaeli J. Comparison of pneumatic dilation with pneumatic dilation plus botulinum toxin for treatment of achalasia. *Acta medica Iranica*. 2010;48(2):107-10.
140. Allescher HD, Storr M, Seige M, Gonzales-Donoso R, Ott R, Born P, et al. Treatment of achalasia: botulinum toxin injection vs. pneumatic balloon dilation. A prospective study with long-term follow-Up. *Endoscopy*. 2001;33(12):1007-17. Epub 2001/12/12.
141. Leyden JE, Moss AC, MacMathuna P. Endoscopic pneumatic dilation versus botulinum toxin injection in the management of primary achalasia. *The Cochrane database of systematic reviews*. 2014(12):CD005046. Epub 2014/12/09.
142. Andrews CN, Anvari M, Dobranowski J. Laparoscopic Heller's myotomy or botulinum toxin injection for management of esophageal achalasia. Patient choice and treatment outcomes. *Surgical endoscopy*. 1999;13(8):742-6. Epub 1999/08/03.
143. Zaninotto G, Annese V, Costantini M, Del Genio A, Costantino M, Epifani M, et al. Randomized controlled trial of botulinum toxin versus laparoscopic heller myotomy for esophageal achalasia. *Annals of surgery*. 2004;239(3):364-70. Epub 2004/04/13.
144. Kostic S, Kjellin A, Ruth M, Lonroth H, Johnsson E, Andersson M, et al. Pneumatic dilatation or laparoscopic cardiomyotomy in the management of newly diagnosed idiopathic achalasia. Results of a randomized controlled trial. *World journal of surgery*. 2007;31(3):470-8. Epub 2007/02/20.
145. Persson J, Johnsson E, Kostic S, Lundell L, Smedh U. Treatment of achalasia with laparoscopic myotomy or pneumatic dilatation: long-term results of a prospective, randomized study. *World journal of surgery*. 2015;39(3):713-20. Epub 2014/11/21.
146. Suarez J, Mearin F, Boque R, Zanon V, Armengol JR, Pradell J, et al. Laparoscopic myotomy vs endoscopic dilation in the treatment of achalasia. *Surgical endoscopy*. 2002;16(1):75-7. Epub 2002/04/19.
147. Novais PA, Lemme EM. 24-h pH monitoring patterns and clinical response after achalasia treatment with pneumatic dilation or laparoscopic Heller myotomy. *Alimentary pharmacology & therapeutics*. 2010;32(10):1257-65. Epub 2010/10/20.
148. Tabola R, Grabowski K, Lewandowski A, Augoff K, Markocka-Maczka K. Achalasia--balloon dilation or surgery? *Medical science monitor : international medical journal of experimental and clinical research*. 2013;19:1089-94. Epub 2013/12/04.

149. Wang HM, Tai WC, Chuah SK, Lu HI, Lu LS, Liang CM, et al. Comparison of treatment outcomes of endoscope-guided pneumatic dilation and laparoscopic Heller myotomy. *The Kaohsiung journal of medical sciences*. 2015;31(12):639-43. Epub 2015/12/29.
150. Hamdy E, El Nakeeb A, El Hanfy E, El Hemaly M, Salah T, Hamed H, et al. Comparative Study Between Laparoscopic Heller Myotomy Versus Pneumatic Dilatation for Treatment of Early Achalasia: A Prospective Randomized Study. *Journal of laparoendoscopic & advanced surgical techniques Part A*. 2015;25(6):460-4. Epub 2015/05/08.
151. Chrystoja CC, Darling GE, Diamant NE, Kortan PP, Tomlinson GA, Deitel W, et al. Achalasia-Specific Quality of Life After Pneumatic Dilation or Laparoscopic Heller Myotomy With Partial Fundoplication: A Multicenter, Randomized Clinical Trial. *The American journal of gastroenterology*. 2016;111(11):1536-45. Epub 2016/11/04.
152. Vela MF, Richter JE, Khandwala F, Blackstone EH, Wachsberger D, Baker ME, et al. The long-term efficacy of pneumatic dilatation and Heller myotomy for the treatment of achalasia. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2006;4(5):580-7. Epub 2006/04/25.
153. Harvey PR, Coupland B, Mytton J, Evison F, Patel P, Trudgill NJ. Outcomes of pneumatic dilatation and Heller's myotomy for achalasia in England between 2005 and 2016. *Gut*. 2019;68(7):1146-51. Epub 2019/01/05.
154. Karanicolas PJ, Smith SE, Inculet RI, Malthaner RA, Reynolds RP, Goeree R, et al. The cost of laparoscopic myotomy versus pneumatic dilatation for esophageal achalasia. *Surgical endoscopy*. 2007;21(7):1198-206. Epub 2007/05/05.
155. Gray RT, Coleman HG, Lau KW, McCaughey C, Coyle PV, Murray LJ, et al. Heller's myotomy and pneumatic dilatation in the treatment of achalasia: a population-based case-control study assessing long-term quality of life. *Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus*. 2017;30(3):1-7. Epub 2015/11/07.
156. Csendes A, Velasco N, Braghetto I, Henriquez A. A prospective randomized study comparing forceful dilatation and esophagomyotomy in patients with achalasia of the esophagus. *Gastroenterology*. 1981;80(4):789-95. Epub 1981/04/01.
157. Csendes A, Braghetto I, Henriquez A, Cortes C. Late results of a prospective randomised study comparing forceful dilatation and oesophagomyotomy in patients with achalasia. *Gut*. 1989;30(3):299-304. Epub 1989/03/01.
158. Cheng JW, Li Y, Xing WQ, Lv HW, Wang HR. Laparoscopic Heller myotomy is not superior to pneumatic dilation in the management of primary achalasia: Conclusions of a systematic review and meta-analysis of randomized controlled trials. *Medicine*. 2017;96(7):e5525. Epub 2017/02/17.
159. Illes A, Farkas N, Hegyi P, Garami A, Szabo I, Solymar M, et al. Is Heller myotomy better than balloon dilation? A meta-analysis. *Journal of gastrointestinal and liver diseases : JGLD*. 2017;26(2):121-7. Epub 2017/06/16.
160. Baniya R, Upadhaya S, Khan J, Subedi SK, Shaik Mohammed T, Ganatra BK, et al. Laparoscopic esophageal myotomy versus pneumatic dilation in the treatment of idiopathic achalasia: a meta-analysis of randomized controlled trials. *Clinical and experimental gastroenterology*. 2017;10:241-8. Epub 2017/10/14.
161. Bonifacio P, de Moura DTH, Bernardo WM, de Moura ETH, Farias GFA, Neto ACM, et al. Pneumatic dilation versus laparoscopic Heller's myotomy in the treatment of achalasia: systematic review and meta-analysis based on randomized controlled trials. *Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus*. 2019;32(2). Epub 2018/11/01.
162. Yaghoobi M, Mayrand S, Martel M, Roshan-Afshar I, Bijarchi R, Barkun A. Laparoscopic Heller's myotomy versus pneumatic dilation in the treatment of idiopathic achalasia: a meta-analysis of randomized, controlled trials. *Gastrointestinal endoscopy*. 2013;78(3):468-75. Epub 2013/05/21.
163. Schoenberg MB, Marx S, Kersten JF, Rosch T, Belle S, Kahler G, et al. Laparoscopic Heller

- myotomy versus endoscopic balloon dilatation for the treatment of achalasia: a network meta-analysis. *Annals of surgery*. 2013;258(6):943-52. Epub 2013/11/14.
164. Wang L, Li YM, Li L. Meta-analysis of randomized and controlled treatment trials for achalasia. *Digestive diseases and sciences*. 2009;54(11):2303-11. Epub 2008/12/25.
165. de Heer J, Desai M, Boeckxstaens G, Zaninotto G, Fuchs KH, Sharma P, et al. Pneumatic balloon dilatation versus laparoscopic Heller myotomy for achalasia: a failed attempt at meta-analysis. *Surgical endoscopy*. 2020. Epub 2020/03/18.
166. Wang X, Tan Y, Lv L, Zhu H, Chu Y, Li C, et al. Peroral endoscopic myotomy versus pneumatic dilation for achalasia in patients aged \geq 65 years. *Revista espanola de enfermedades digestivas : organo oficial de la Sociedad Espanola de Patologia Digestiva*. 2016;108(10):637-41. Epub 2016/09/22.
167. Meng F, Li P, Wang Y, Ji M, Wu Y, Yu L, et al. Peroral endoscopic myotomy compared with pneumatic dilation for newly diagnosed achalasia. *Surgical endoscopy*. 2017;31(11):4665-72. Epub 2017/04/16.
168. Ponds FA, Fockens P, Lei A, Neuhaus H, Beyna T, Kandler J, et al. Effect of Peroral Endoscopic Myotomy vs Pneumatic Dilation on Symptom Severity and Treatment Outcomes Among Treatment-Naive Patients With Achalasia: A Randomized Clinical Trial. *Jama*. 2019;322(2):134-44. Epub 2019/07/10.
169. Yadlapati R, Gupta S. Peroral Endoscopic Myotomy versus Pneumatic Dilation in Achalasia: Dissecting the Randomized Controlled Trial. *Gastroenterology*. 2020;158(1):276-7. Epub 2019/11/11.
170. Zhong C, Tan S, Huang S, Lu M, Peng Y, Fu X, et al. Peroral endoscopic myotomy versus pneumatic dilation for achalasia: a systematic review and meta-analysis. *European journal of gastroenterology & hepatology*. 2020;32(11):1413-21.
171. Ramirez M, Zubieta C, Ciotola F, Amenabar A, Badaloni A, Nachman F, et al. Per oral endoscopic myotomy vs. laparoscopic Heller myotomy, does gastric extension length matter? *Surgical endoscopy*. 2018;32(1):282-8.
172. Hanna AN, Datta J, Ginzberg S, Dasher K, Ginsberg GG, Dempsey DT. Laparoscopic Heller Myotomy vs Per Oral Endoscopic Myotomy: Patient-Reported Outcomes at a Single Institution. *Journal of the American College of Surgeons*. 2018;226(4):465-72 e1.
173. Peng L, Tian S, Du C, Yuan Z, Guo M, Lu L. Outcome of Peroral Endoscopic Myotomy (POEM) for Treating Achalasia Compared With Laparoscopic Heller Myotomy (LHM). *Surgical laparoscopy, endoscopy & percutaneous techniques*. 2017;27(1):60-4.
174. Leeds SG, Burdick JS, Ogola GO, Ontiveros E. Comparison of outcomes of laparoscopic Heller myotomy versus per-oral endoscopic myotomy for management of achalasia. *Proceedings*. 2017;30(4):419-23.
175. Khashab MA, Kumbhari V, Tieu AH, El Zein MH, Ismail A, Ngamruengphong S, et al. Peroral endoscopic myotomy achieves similar clinical response but incurs lesser charges compared to robotic heller myotomy. *Saudi journal of gastroenterology : official journal of the Saudi Gastroenterology Association*. 2017;23(2):91-6.
176. de Pascale S, Repici A, Puccetti F, Carlani E, Rosati R, Fumagalli U. Peroral endoscopic myotomy versus surgical myotomy for primary achalasia: single-center, retrospective analysis of 74 patients. *Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus*. 2017;30(8):1-7.
177. Schneider AM, Louie BE, Warren HF, Farivar AS, Schembre DB, Aye RW. A Matched Comparison of Per Oral Endoscopic Myotomy to Laparoscopic Heller Myotomy in the Treatment of Achalasia. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract*. 2016;20(11):1789-96.
178. Sanaka MR, Hayat U, Thota PN, Jegadeesan R, Ray M, Gabbard SL, et al. Efficacy of peroral endoscopic myotomy vs other achalasia treatments in improving esophageal function. *World journal of gastroenterology*. 2016;22(20):4918-25.
179. Teitelbaum EN, Rajeswaran S, Zhang R, Sieberg RT, Miller FH, Soper NJ, et al. Peroral esophageal myotomy (POEM) and laparoscopic Heller myotomy produce a similar short-term anatomic and functional effect. *Surgery*. 2013;154(4):885-91; discussion 91-2.

180. Vigneswaran Y, Yetasook AK, Zhao JC, Denham W, Linn JG, Ujiki MB. Peroral endoscopic myotomy (POEM): feasible as reoperation following Heller myotomy. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract*. 2014;18(6):1071-6.
181. Hungness ES, Teitelbaum EN, Santos BF, Arafat FO, Pandolfino JE, Kahrilas PJ, et al. Comparison of perioperative outcomes between peroral esophageal myotomy (POEM) and laparoscopic Heller myotomy. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract*. 2013;17(2):228-35.
182. Bhayani NH, Kurian AA, Dunst CM, Sharata AM, Rieder E, Swanstrom LL. A comparative study on comprehensive, objective outcomes of laparoscopic Heller myotomy with per-oral endoscopic myotomy (POEM) for achalasia. *Annals of surgery*. 2014;259(6):1098-103.
183. Ujiki MB, Yetasook AK, Zapf M, Linn JG, Carbray JM, Denham W. Peroral endoscopic myotomy: A short-term comparison with the standard laparoscopic approach. *Surgery*. 2013;154(4):893-7; discussion 7-900.
184. Docimo S, Jr., Mathew A, Shope AJ, Winder JS, Haluck RS, Pauli EM. Reduced postoperative pain scores and narcotic use favor per-oral endoscopic myotomy over laparoscopic Heller myotomy. *Surgical endoscopy*. 2017;31(2):795-800.
185. Kumbhari V, Familiari P, Bjerregaard NC, Pioche M, Jones E, Ko WJ, et al. Gastroesophageal reflux after peroral endoscopic myotomy: a multicenter case-control study. *Endoscopy*. 2017;49(7):634-42.
186. Repici A, Fuccio L, Maselli R, Mazza F, Correale L, Mandolesi D, et al. GERD after per-oral endoscopic myotomy as compared with Heller's myotomy with fundoplication: a systematic review with meta-analysis. *Gastrointestinal endoscopy*. 2018;87(4):934-43 e18.
187. Schlottmann F, Luckett DJ, Fine J, Shaheen NJ, Patti MG. Laparoscopic Heller Myotomy Versus Peroral Endoscopic Myotomy (POEM) for Achalasia: A Systematic Review and Meta-analysis. *Annals of surgery*. 2018;267(3):451-60.
188. Marano L, Pallabazzer G, Solito B, Santi S, Pigazzi A, De Luca R, et al. Surgery or Peroral Esophageal Myotomy for Achalasia: A Systematic Review and Meta-Analysis. *Medicine*. 2016;95(10):e3001.
189. Zhang Y, Wang H, Chen X, Liu L, Wang H, Liu B, et al. Per-Oral Endoscopic Myotomy Versus Laparoscopic Heller Myotomy for Achalasia: A Meta-Analysis of Nonrandomized Comparative Studies. *Medicine*. 2016;95(6):e2736.
190. Talukdar R, Inoue H, Nageshwar Reddy D. Efficacy of peroral endoscopic myotomy (POEM) in the treatment of achalasia: a systematic review and meta-analysis. *Surgical endoscopy*. 2015;29(11):3030-46.
191. Awaiz A, Yunus RM, Khan S, Memon B, Memon MA. Systematic Review and Meta-Analysis of Perioperative Outcomes of Peroral Endoscopic Myotomy (POEM) and Laparoscopic Heller Myotomy (LHM) for Achalasia. *Surgical laparoscopy, endoscopy & percutaneous techniques*. 2017;27(3):123-31.
192. Martins RK, Ribeiro IB, DTH DEM, Hathorn KE, Bernardo WM, EGH DEM. Peroral (Poem) or Surgical Myotomy for the Treatment of Achalasia: A Systematic Review and Meta-Analysis. *Arquivos de gastroenterologia*. 2020;57(1):79-86.
193. Park CH, Jung DH, Kim DH, Lim CH, Moon HS, Park JH, et al. Comparative efficacy of per-oral endoscopic myotomy and Heller myotomy in patients with achalasia: a meta-analysis. *Gastrointestinal endoscopy*. 2019;90(4):546-58 e3.
194. Mundre P, Black CJ, Mohammed N, Ford AC. Efficacy of surgical or endoscopic treatment of idiopathic achalasia: a systematic review and network meta-analysis. *The lancet Gastroenterology & hepatology*. 2021;6(1):30-8.
195. Aiolfi A, Bona D, Riva CG, Micheletto G, Rausa E, Campanelli G, et al. Systematic Review and Bayesian Network Meta-Analysis Comparing Laparoscopic Heller Myotomy, Pneumatic Dilatation, and Peroral Endoscopic Myotomy for Esophageal Achalasia. *Journal of laparoendoscopic & advanced surgical techniques Part A*. 2020;30(2):147-55.

Chapter 5

DIAGNOSIS OF ACHALASIA

Hakan ÇAMYAR¹

INTRODUCTION

Achalasia is a disorder that affects the esophagus due to incomplete relaxation of the lower esophageal sphincter (LES). Although new diagnostic and treatment methods have evolved in the last decades, it is one of the oldest described diseases in the literature. Thomas Willis described it in 1674 and tried whalebone to relieve dysphagia related to non-relaxation of the esophagus. Hertz created the term “achalasia” from the Greek term that means “non-relaxing” because he proposed that the disease is a result of the incomplete relaxation of LES rather than the spasm of the esophagus (1).

Although achalasia is a prototype of primary esophageal motor disorder, it is a rare disease except for the endemic form of achalasia seen during Chagas disease caused by the parasite *Trypanosoma cruzi* in South America. Achalasia is divided into two types, the primary type and secondary or pseudo achalasia (PA). Primary type achalasia, named idiopathic achalasia (IA) because of its uncertainty about etiology, is seen with approximately 1 per 100000 persons per year (2). After the wide use of high-resolution manometers (HRM), the incidence of achalasia has increased to 2.3 - 2.92 per 100000 persons per year (3).

Both the diagnosis of and treatment of achalasia have been tremendously challenged with the advent of HRM and the introduction of peroral endoscopic myotomy (POEM), respectively. These two new developments have caused great concern for the clinical approach to achalasia. Two gastroenterology societies published the new version of their achalasia guidelines in 2020 (4, 5).

Pathophysiology and Natural Course

The fundamental problem in achalasia is the degeneration of the neuronal esophageal plexus that causes incomplete relaxation of LES and ineffective contraction in the esophagus body. Despite new insights in physiology, there is still debate on what starts the degeneration. Inflammatory infiltration predominantly

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REFERENCES

- 1.Hertz AF. Achalasia of the Cardia (so-called Cardio-spasm). Proceedings of the Royal Society of Medicine. 1915;8(Clin Sect):22-5. Epub 1915/01/01.
- 2.Sadowski DC, Ackah F, Jiang B, Svenson LW. Achalasia: incidence, prevalence, and survival. A population-based study. *Neurogastroenterology and motility: the official journal of the European Gastrointestinal Motility Society*. 2010;22(9):e256-61. Epub 2010/05/15.
- 3.Duffield JA, Hamer PW, Heddle R, Holloway RH, Myers JC, Thompson SK. Incidence of Achalasia in South Australia Based on Esophageal Manometry Findings. *Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association*. 2017;15(3):360-5. Epub 2016/06/09.
- 4.Vaezi MF, Pandolfino JE, Yadlapati RH, Greer KB, Kavitt RT. ACG Clinical Guidelines: Diagnosis and Management of Achalasia. *The American Journal of gastroenterology*. 2020;115(9):1393-411.
- 5.Khashab MA, Vela MF, Thosani N, Agrawal D, Buxbaum JL, Abbas Fehmi SM, et al. ASGE guideline on the management of achalasia. *Gastrointestinal endoscopy*. 2020;91(2):213-27 e6.
- 6.Clark SB, Rice TW, Tubbs RR, Richter JE, Goldblum JR. The nature of the myenteric infiltrates in achalasia: an immunohistochemical analysis. *The American Journal of surgical pathology*. 2000;24(8):1153-8. Epub 2000/08/10.
- 7.Verne GN, Sallustio JE, Eaker EY. Anti-myenteric neuronal antibodies in patients with achalasia. A prospective study. *Digestive diseases and sciences*. 1997;42(2):307-13.
- 8.Moses PL, Ellis LM, Anees MR, Ho W, Rothstein RI, Meddings JB, et al. Antineuronal antibodies in idiopathic achalasia and gastro-oesophageal reflux disease. *Gut*. 2003;52(5):629-36.
- 9.Niwamoto H, Okamoto E, Fujimoto J, Takeuchi M, Furuyama J, Yamamoto Y. Are human herpes viruses or measles virus associated with esophageal achalasia? *Digestive diseases and sciences*. 1995;40(4):859-64.
- 10.Birgisson S, Galinski MS, Goldblum JR, Rice TW, Richter JE. Achalasia is not associated with measles or known herpes and human papillomaviruses. *Digestive diseases and sciences*. 1997;42(2):300-6.
- 11.Kinoshita Y, Oouchi S, Fujisawa T. Eosinophilic gastrointestinal diseases - Pathogenesis, diagnosis, and treatment. *Allergy international: official Journal of the Japanese Society of Allergology*. 2019;68(4):420-9.
- 12.Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA, et al. ACG clinical guideline: Evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *The American Journal of gastroenterology*. 2013;108(5):679-92; quiz 93.
- 13.Nakajima N, Sato H, Takahashi K, Hasegawa G, Mizuno K, Hashimoto S, et al. Muscle layer histopathology and manometry pattern of primary esophageal motility disorders including achalasia. *Neurogastroenterol Motil*. 2017;29(3).
- 14.Tottrup A, Fredens K, Funch-Jensen P, Aggestrup S, Dahl R. Eosinophil infiltration in primary esophageal achalasia. A possible pathogenic role. *Digestive diseases and sciences*. 1989;34(12):1894-9.
- 15.Rieder E, Fernandez-Becker NQ, Sarosiek J, Guillaume A, Azagury DE, Clarke JO. Achalasia: physiology and diagnosis. *Annals of the New York Academy of Sciences*. 2020.
- 16.Park W, Vaezi MF. Etiology and pathogenesis of achalasia: the current understanding. *The American Journal of gastroenterology*. 2005;100(6):1404-14.
- 17.Csendes A, Smok G, Braghetto I, Gonzalez P, Henriquez A, Csendes P, et al. Histological studies of Auerbach's plexuses of the esophagus, stomach, jejunum, and colon in patients with achalasia of the esophagus: correlation with gastric acid secretion, presence of parietal cells and gastric emptying of solids. *Gut*. 1992;33(2):150-4.
- 18.Fei L, Rossetti G, Moccia F, Cimmino M, Guerriero L, Romano G, et al. Definition, incidence and etiology: what's new in the 21st century? *Annali italiani di chirurgia*. 2013;84(5):489-94.

- 19.Kahrilas PJ, Boeckstaens G. The spectrum of achalasia: lessons from studies of pathophysiology and high-resolution manometry. *Gastroenterology*. 2013;145(5):954-65. Epub 2013/08/27.
- 20.Richter JE. The diagnosis and misdiagnosis of achalasia: it does not have to be so difficult. *Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association*. 2011;9(12):1010-1.
- 21.Salvador R, Voltarel G, Savarino E, Capovilla G, Pesenti E, Perazzolo A, et al. The natural history of achalasia: Evidence of a continuum-”The evolutive pattern theory”. *Digestive and liver disease: official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver*. 2018;50(4):342-7.
- 22.Shoenut JP, Micflikier AB, Yaffe CS, Den Boer B, Teskey JM. Reflux in untreated achalasia patients. *Journal of clinical gastroenterology*. 1995;20(1):6-11.
- 23.Frankhuisen R, van Herwaarden MA, Heijkoop R, Smout AJ, Baron A, Vermeijden JR, et al. Persisting symptoms and decreased health-related quality-of-life in a cross-sectional study of treated achalasia patients. *Alimentary pharmacology & therapeutics*. 2007;26(6):899-904.
- 24.Newberry C, Vajravelu RK, Pickett-Blakely O, Falk G, Yang YX, Lynch KL. Achalasia Patients Are at Nutritional Risk Regardless of Presenting Weight Category. *Digestive diseases and sciences*. 2018;63(5):1243-9.
- 25.Harvey PR, Thomas T, Chandan JS, Mytton J, Coupland B, Bhala N, et al. Incidence, morbidity and mortality of patients with achalasia in England: findings from a study of nationwide hospital and primary care data. *Gut*. 2019;68(5):790-5.
- 26.Eckardt VF. Clinical presentations and complications of achalasia. *Gastrointestinal endoscopy clinics of North America*. 2001;11(2):281-92, vi.
- 27.Taft TH, Carlson DA, Triggs J, Craft, J, Starkey K, Yadlapati, R, et al. Evaluating the reliability and construct validity of the Eckardt symptom score as a measure of achalasia severity. *Neurogastroenterol Motil*. 2018;30(6):e13287.
- 28.El-Takli I, O'Brien P, Paterson WG. Clinical diagnosis of achalasia: how reliable is the barium x-ray? *Canadian Journal of gastroenterology = Journal canadien de gastroenterologie*. 2006;20(5):335-7.
- 29.de Oliveira JM, Birgisson S, Doinoff C, Einstein D, Herts B, Davros W, et al. Timed barium swallow: a simple technique for evaluating esophageal emptying in patients with achalasia. *AJR American journal of roentgenology*. 1997;169(2):473-9. Epub 1997/08/01.
- 30.Vaezi MF, Baker ME, Richter JE. Assessment of esophageal emptying post-pneumatic dilation: use of the timed barium esophagram. *The American Journal of gastroenterology*. 1999;94(7):1802-7. Epub 1999/07/16.
- 31.Feczko PJ, Halpert RD. Achalasia secondary to nongastrointestinal malignancies. *Gastrointestinal radiology*. 1985;10(3):273-6. Epub 1985/01/01.
- 32.Jia Y, McCallum RW. Pseudoachalasia: Still a Tough Clinical Challenge. *The American Journal of case reports*. 2015;16:768-73. Epub 2015/10/30.
- 33.Li SW, Tseng PH, Chen CC, Liao WC, Liu KL, Lee JM, et al. Muscular thickness of lower esophageal sphincter and therapeutic outcomes in achalasia: A prospective study using high-frequency endoscopic ultrasound. *Journal of gastroenterology and hepatology*. 2018;33(1):240-8. Epub 2017/05/06.
- 34.Hoshikawa Y, Hoshino S, Kawami N, Tanabe T, Hanada Y, Takenouchi N, et al. Possible new endoscopic finding in patients with achalasia: “Ginkgo leaf sign”. *Esophagus: Official Journal of the Japan Esophageal Society*. 2020;17(2):208-13. Epub 2019/06/23.
- 35.Cappell MS, Stavropoulos SN, Friedel D. Updated Systematic Review of Achalasia, with a Focus on POEM Therapy. *Digestive diseases and sciences*. 2020;65(1):38-65.
- 36.Soudagar AS, Sayuk GS, Gyawali CP. Learners favor high resolution oesophageal manometry with better diagnostic accuracy over conventional line tracings. *Gut*. 2012;61(6):798-803. Epub 2011/10/15.
- 37.Roman S, Huot L, Zerbib F, Bruley des Varannes S, Gourcerol G, Coffin B, et al. High-Resolution Manometry Improves the Diagnosis of Esophageal Motility Disorders in Patients With

- Dysphagia: A Randomized Multicenter Study. *The American Journal of gastroenterology*. 2016;111(3):372-80. Epub 2016/02/03.
38. Carlson DA, Ravi K, Kahrilas PJ, Gyawali CP, Bredenoord AJ, Castell DO, et al. Diagnosis of Esophageal Motility Disorders: Esophageal Pressure Topography vs. Conventional Line Tracing. *The American Journal of gastroenterology*. 2015;110(7):967-77; quiz 78. Epub 2015/06/03.
39. Roman S, Gyawali CP, Xiao Y, Pandolfino JE, Kahrilas PJ. The Chicago classification of motility disorders: an update. *Gastrointestinal endoscopy clinics of North America*. 2014;24(4):545-61. Epub 2014/09/14.
40. Pandolfino JE, Kwiatek MA, Nealis T, Bulsiewicz W, Post J, Kahrilas PJ. Achalasia: a new clinically relevant classification by high-resolution manometry. *Gastroenterology*. 2008;135(5):1526-33. Epub 2008/08/30.
41. Andolfi C, Fisichella PM. Meta-analysis of clinical outcome after treatment for achalasia based on manometric subtypes. *The British Journal of surgery*. 2019;106(4):332-41.
42. Scherer JR, Kwiatek MA, Soper NJ, Pandolfino JE, Kahrilas PJ. Functional esophagogastric junction obstruction with intact peristalsis: a heterogeneous syndrome sometimes akin to achalasia. *Journal of gastrointestinal surgery: official Journal of the Society for Surgery of the Alimentary Tract*. 2009;13(12):2219-25. Epub 2009/08/13.
43. Herbella FA, Oliveira DR, Del Grande JC. Are idiopathic and Chagasic achalasia two different diseases? *Digestive diseases and sciences*. 2004;49(3):353-60. Epub 2004/05/14.
44. Schlottmann F, Patti MG. Primary Esophageal Motility Disorders: Beyond Achalasia. *International Journal of molecular sciences*. 2017;18(7). Epub 2017/07/01.
45. Carlson DA, Hirano I. Application of the Functional Lumen Imaging Probe to Esophageal Disorders. *Current treatment options in gastroenterology*. 2017;15(1):10-25. Epub 2017/03/08.
46. Carlson DA, Kahrilas PJ, Lin Z, Hirano I, Gonsalves N, Listernick Z, et al. Evaluation of Esophageal Motility Utilizing the Functional Lumen Imaging Probe. *The American Journal of gastroenterology*. 2016;111(12):1726-35. Epub 2016/10/12.
47. Chang J, Yoo IK, Gunay S, Pakoz ZB, Cho JY. Clinical usefulness of esophagogastric junction distensibility measurement in patients with achalasia before and after peroral endoscopic myotomy. *The Turkish Journal of gastroenterology: the Official Journal of Turkish Society of Gastroenterology*. 2020;31(5):362-7. Epub 2020/06/11.
48. Rohof WO, Hirsch DP, Kessing BF, Boeckxstaens GE. Efficacy of treatment for patients with achalasia depends on the distensibility of the esophagogastric junction. *Gastroenterology*. 2012;143(2):328-35. Epub 2012/05/09.

Chapter 6

CURRENT APPROACH TO DIABETIC KETOACIDOSIS

Çilem ÇALTILI¹

INTRODUCTION AND EPIDEMIOLOGY

Diabetes can cause defects in carbohydrate, fat and protein metabolism steps; It is a chronic metabolism disorder that occurs due to insulin deficiency or insulin secretion and effect disorder (1). Its frequency is increasing in the world. According to the International Diabetes Atlas 9th Report, it was determined that there are 463 million diabetic patients worldwide in 2019. This figure is expected to rise to 578 million in 2030 and 700 million in 2045, according to 2019 data from the International Diabetes Federation (IDF). Turkey has also got to go to correlate data with international data in the 20-79 age range is approximately 7 million diabetics present covers 15% of the population.

Diabetic ketoacidosis (DKA), one of the acute complications of diabetes, is frequently seen in patients with type 1 diabetes, but it is the most important life-threatening complication. The most common cause of mortality in the childhood and adolescent type 1 diabetes group is DKA (2-4). However, the frequency of DKA is gradually increasing in newly diagnosed type 2 diabetes patients. In this group defined as prone to ketosis, the most important disorder is observed in the steps in the recovery process of insulin secretion and ketosis (5). Catabolic processes such as trauma and infection increase the susceptibility of type 2 diabetes to ketoacidosis (6,7).

In developing countries, especially in middle-aged and elderly patients with comorbidity, mortality rates due to DKA are quite high (8).

Patophysiology

The main pathophysiology in DKA is relative insulin deficiency and excess of hormones involved in contraregulatory or cell catabolism (Figure 1). Insulin is the only anabolic endocrine hormone produced by the pancreas. Contraregulatory hormones are glucagon, corticosteroids, growth hormone and catecholami-

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ase in pharmaceutical products in the world market has brought about the increase in drug consumption and drug expenditures. For this reason, the importance of rational drug use, which is defined as “planning, execution and monitoring process that enables the effective, safe and economical implementation of drug therapy”, is constantly increasing.

REFERENCES

1. Conference of Experts on the Rational Use of Drugs, World Health Organization, Nairobi, Kenya, WHO/CONRAD/WP/RI, (25-29.12.1985)
2. Aslam B, Wang W, Arshad MI, et al. Antibiotic resistance: a rundown of a global crisis. *Infection and Drug Resistance*, 2018;11, 1645—1658 Doi: 10.2147/IDR.S173867
3. Torre NF, Solomon VP, Middleton LE. Identifying the commonly used antibiotics for self-medication in urban Mozambique: a qualitative study. *BMJ Open*, 2020;10:e041323. Doi: 10.1136/bmjopen-2020-041323
4. Mollahaliloglu S, Alkan A, Donertas B, et al. Assessment of antibiotic prescribing at different hospitals and primary health care facilities, *Saudi Pharmaceutical Journal* 2013;21(3), 281-291 Doi: 10.1016/j.jsps.2012.10.004
5. Wright GD, Tyers M. Drug combinations: a strategy to extend the life of antibiotics in the 21st century. *Nature Reviews Microbiology*, 2019;17, 141-155 Doi: 10.1038/s41579-018-0141-x
6. Evans DG, Thomas S, Caunt J, et al. Rational drug use – As common as common sense?, *Medical Journal Armed Forces India*, 2012; 68(3), 206-208 doi: 10.1016/j.mjafi.2012.04.002
7. Dixon J, Manyau S, Kandiye F, et al. Antibiotics, rational drug use and the architecture of global health in Zimbabwe, *Social Science & Medicine*, 2021; 272: 113594 Doi: 10.1016/j.socsci-med.2020.113594
8. Rowe TA, Linder JA. Novel approaches to decrease inappropriate ambulatory antibiotic use, *Expert Rev Anti Infect Ther*, 2019;17(7):511-521. doi: 10.1080/14787210.2019.1635455
9. Sipahi OR. Economics of antibiotic resistance, *Expert Review of Anti-infective Therapy*, 2014; 12(3), 165-170 Doi: 10.1586/14787210.6.4.523
10. Öztürk R. (2008). *Toplumdan Edinilmiş Enfeksiyonlara Pratik Yaklaşımlar*. İstanbul, İ.Ü. Cerrahpaşa Tıp Fakültesi Sürekli Tıp Eğitimi Etkinlikleri
11. Kef K. Edirne ilinde tedaviye dirençli kronik otitte kültür antibiyogram sonuçları, *Namık Kemal Tıp Dergisi*, 2019;7(3), 253-258
12. Gökçe H, Gürdoğan EP. Complementary and Alternative Therapy Usage Status and Attitudes of Hypertension Patients. *Euras J Fam Med*, 2019;8(2):59-68. doi:10.33880/ejfm.2019080202
13. Kef K, Muluk NB, Konstantinidis I, Scadding GK. (2020) Recent Combination Therapy Options for Allergic Rhinitis, Challenges in Rhinology pp 75-82, Switzerland, Springer Nature
14. Hartmann B, Czock D, Keller F. Drug therapy in patients with chronic renal failure, *Dtsch Arztebl Int*. 2010;107(37): 647–656 Doi: 10.3238/arztebl.2010.0647
15. Muanda FT, Sheehy O, Bérard A. Use of antibiotics during pregnancy and the risk of major congenital malformations: a population based cohort study. *Br J Clin Pharmacol*. 2017; 83(11): 2557–2571 Doi: 10.1111/bcp.13364

Chapter 7

RATIONAL DRUG USE

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Use of drugs has a major role in the healthcare system. Increasing knowledge and technological advances have made it possible to treat a wider range of diseases and improved already existing treatment modalities. The need for drug use has increased rapidly alongside the world population. The need to develop new drugs has emerged. For all these reasons, the rational use of drugs has become crucial. The term “rational drug use” was first used by the World Health Organization in 1985. (1)

Misuse of drugs, especially antibiotics, both complicates treatments and causes economic losses. (2) The budget requirements for medicine constitute a serious burden on the expenditures of social security institutions all over the world. Antibiotics are one of the most commonly used drug groups in medicine. They are also one of the most commonly misused drug groups. (3-5) Since infections can develop in every organ of the human body, all physicians should be well aware of the use of antibiotics. Due to reasons such as the development of resistance to antibiotics and the introduction of new antibiotics in the treatment, it is necessary to continuously renew the knowledge.

It is the proper dosage and the rational use that separates drugs from poison.

Rational use of antibiotics can be defined as the ability to easily provide the appropriate drug in the appropriate time, at the appropriate dose, with the lowest side effects and lowest costs according to the clinical findings, individual characteristics, disease agent, and resistance of the people. (6,7)

Rational use of antibiotics significantly affects the success of the treatment, survival rates, the development of complications, and prevention of chronicity, duration and severity of the disease. Despite these positive effects, unfortunately, irrational drug use is still too much. Even in the USA, where drug use mechanisms are applied most intensely and severely, up to 50% of inappropriate antibiotic use occurs. (8)

Inappropriate antibiotic use causes the development of resistance as well as harming the patient due to its side effects. It also causes serious economic damage all over the world. Therefore, rational use of antibiotics is very important in terms

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ase in pharmaceutical products in the world market has brought about the increase in drug consumption and drug expenditures. For this reason, the importance of rational drug use, which is defined as “planning, execution and monitoring process that enables the effective, safe and economical implementation of drug therapy”, is constantly increasing.

REFERENCES

1. Conference of Experts on the Rational Use of Drugs, World Health Organization, Nairobi, Kenya, WHO/CONRAD/WP/RI, (25-29.12.1985)
2. Aslam B, Wang W, Arshad MI, et al. Antibiotic resistance: a rundown of a global crisis. *Infection and Drug Resistance*, 2018;11, 1645—1658 Doi: 10.2147/IDR.S173867
3. Torre NF, Solomon VP, Middleton LE. Identifying the commonly used antibiotics for self-medication in urban Mozambique: a qualitative study. *BMJ Open*, 2020;10:e041323. Doi: 10.1136/bmjopen-2020-041323
4. Mollahaliloglu S, Alkan A, Donertas B, et al. Assessment of antibiotic prescribing at different hospitals and primary health care facilities, *Saudi Pharmaceutical Journal* 2013;21(3), 281-291 Doi: 10.1016/j.jsps.2012.10.004
5. Wright GD, Tyers M. Drug combinations: a strategy to extend the life of antibiotics in the 21st century. *Nature Reviews Microbiology*, 2019;17, 141-155 Doi: 10.1038/s41579-018-0141-x
6. Evans DG, Thomas S, Caunt J, et al. Rational drug use – As common as common sense?, *Medical Journal Armed Forces India*, 2012; 68(3), 206-208 doi: 10.1016/j.mjafi.2012.04.002
7. Dixon J, Manyau S, Kandiye F, et al. Antibiotics, rational drug use and the architecture of global health in Zimbabwe, *Social Science & Medicine*, 2021; 272: 113594 Doi: 10.1016/j.socsci-med.2020.113594
8. Rowe TA, Linder JA. Novel approaches to decrease inappropriate ambulatory antibiotic use, *Expert Rev Anti Infect Ther*, 2019;17(7):511-521. doi: 10.1080/14787210.2019.1635455
9. Sipahi OR. Economics of antibiotic resistance, *Expert Review of Anti-infective Therapy*, 2014; 12(3), 165-170 Doi: 10.1586/14787210.6.4.523
10. Öztürk R. (2008). *Toplumdan Edinilmiş Enfeksiyonlara Pratik Yaklaşımlar*. İstanbul, İ.Ü. Cerrahpaşa Tıp Fakültesi Sürekli Tıp Eğitimi Etkinlikleri
11. Kef K. Edirne ilinde tedaviye dirençli kronik otitte kültür antibiyogram sonuçları, *Namık Kemal Tıp Dergisi*, 2019;7(3), 253-258
12. Gökçe H, Gürdoğan EP. Complementary and Alternative Therapy Usage Status and Attitudes of Hypertension Patients. *Euras J Fam Med*, 2019;8(2):59-68. doi:10.33880/ejfm.2019080202
13. Kef K, Muluk NB, Konstantinidis I, Scadding GK. (2020) Recent Combination Therapy Options for Allergic Rhinitis, Challenges in Rhinology pp 75-82, Switzerland, Springer Nature
14. Hartmann B, Czock D, Keller F. Drug therapy in patients with chronic renal failure, *Dtsch Arztebl Int*. 2010;107(37): 647–656 Doi: 10.3238/arztebl.2010.0647
15. Muanda FT, Sheehy O, Bérard A. Use of antibiotics during pregnancy and the risk of major congenital malformations: a population based cohort study. *Br J Clin Pharmacol*. 2017; 83(11): 2557–2571 Doi: 10.1111/bcp.13364

Chapter 8

MALNUTRITION IN THE ELDERLY; APPROACH TO NUTRITION PRINCIPLES AND BIOCHEMICAL PROPERTIES IN ALL ASPECTS

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INTRODUCTION

With the innovations made in the field of health in the developing world, the human life has extended and the number of people over the age of 60 has increased rapidly all over the world. It is predicted that this age group includes approximately 10% of the world society or approximately 600 million people in 1999, and this ratio will increase to 20% or reach 2 billion people in 2050. Especially in developed and developing countries, the decrease in birth rates as well as the prolongation of life expectancy in old age relatively causes the share of the elderly population. The fastest growing segment of the population in the United States is people aged 85 or over.(1) Currently, the majority in that life expectancy in Turkey's young population with increasing health facilities, the average increased up to 69 years. Technology and advanced facilities in Turkey in line with the number of elderly people is increasing with each passing day. elderly population in Turkey, while in the year 1935 628.041 people were 7,550,727 people in 2019. The proportion of the elderly population in the total population is said to have increased 2.3 times compared to 1935 and reached 9.1% in 2019. (2)

The population estimates made indicate that this increase trend in the elderly population will continue. According to studies on population, the elderly population ratio is predicted to be 10.2% in 2023, 12.9% in 2030, 16.3% in 2040, 22.6% in 2060 and 25.6% in 2080. (2)

After neurological diseases, which are the most common geriatric syndromes in the elderly, another geriatric syndrome that is most frequently encountered is nutritional disorders. Elderly individuals need to be well nourished in order to lead a quality life. During the aging process, there are some changes in body composition and organ functions. However, changes occur in energy need and

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patients should be treated. The most important problem is in the recognition of malnutrition, because screening all elderly patients is a very difficult and time consuming task. If scans can be integrated into standard applications, the most important obstacle will be removed. Malnutrition is a very common clinical situation in elderly patients who need home healthcare services. Elderly patients in need of home healthcare are a group prone to malnutrition, especially when they have chronic mental or physical illnesses. All elderly patients in need of home healthcare should undergo a comprehensive evaluation, including anamnesis, physical examination, bedside tests evaluating physical and mental functions, and laboratory tests, and should be screened specifically for the risk of malnutrition.

CONCLUSION

Malnutrition is a very common clinical situation in elderly patients who need home healthcare services. Elderly patients in need of home healthcare are a group prone to malnutrition, especially because they have chronic mental or physical illnesses. The world's and Turkey's elderly population is increasing every day. In parallel with this population increase, various effects such as dietary habits, air pollution, genetic factors and diseases related to old age and the nutritional status of the elderly, whose quality of life has decreased, are also deteriorating. Dealing with malnutrition after the emergence of nutritional disorders increases the need for highly difficult and complex treatment methods. In order to prevent this, it is necessary to carry out regular anamnesis, physical examination, bedside tests that evaluate physical and mental functions of elderly patients who need home health care. More important than these measures is the comprehensive and regular biochemical laboratory tests. As a result of our literature review; Important biochemical findings used in the diagnosis and treatment of malnutrition should be considered and monitored. For example, a wide biochemistry panel such as total protein, albumin, hemoglobin, iron, vitamin B-12, folic acid, lymphocyte ratio, ferritin, CRP and sedimentation should be examined periodically. Elderly patients who need home healthcare services should be evaluated with all these scans and should be screened especially in terms of malnutrition risk.

REFERANCES

1. Aksoydan E. Yaşlılık ve Beslenme. Ankara: Burgaz Matbaası, 2005.
2. <https://www.ailevecalisma.gov.tr/media/45354/yasli-nufus-demografik-degisimi-2020>.
3. Morley JE. Anorexia of aging: physiologic and pathologic. *Am J Clin Nutr.* 1997; 66: 760-773.
4. Visvanathan R. Undernutrition in older people: a serious and growing global problem. *J Postgrad Med.* 2003;49(4):352-60.
5. Yeh SS, Schuster MW. Epidemiology of malnutrition in the elderly In: Mantovani G, Anker SD, Inui A, Morley JE, Fanelli FR, Scevola D, et al. editors. *Cachexia and wasting: a modern approach.* Springer Milan; 2006.

6. Saka B. Yaşlı Hastalarda Malnütrisyon. İ.Ü. Cerrahpaşa Tıp Fakültesi Sürekli Tıp Eğitimi Etkinlikleri Sempozyum Dizisi No:75 Geriatrik Hasta ve Sorunları. İstanbul: Doyuran Matbaası. 2011;147-61.
7. Balcı E. 65 Yaş ve Üzeri Bireylerin Depresyon ve Malnutrisyon Durumları Arasındaki İlişki. Türkiye Halk Sağlığı Dergisi. 2012;10 (1): 22-7.
8. De Groot CP, Staveren Wv, Dirren H, et al. Summary and conclusions of the report on the second data collection period and longitudinal analyses of the SENECA Study. Eur J Clin Nutr. 1996;50(Suppl 2):S123-4.
9. Uzundikme F, Çakıroğlu FP. Yaşlılıkta Sebze-Meyve Tüketimi. (Elektronik Sürüm). Ankara: Ankara Üniversitesi Ziraat Fakültesi. 2007
10. Huang Y. Nutrient intakes and iron status of elderly men and women. Nutrition Research.2001; 21(7), 967-981.
11. World Health Organisation. The uses of epidemiology in the study of the elderly (WHO Technical Report Series, No: 706). World Health Organisation. 1984.
12. Aslan D. Yaşlılık Döneminde Sağlıklı Olmak ve Hastalıklardan Korunmak. Y. G. Kutsal (GEBAM), T. Altınok (Keçiören Belediyesi) (Haz.). Sağlıkla ve Üretken Yaşlanalım (s. 11). Ankara: Hacettepe Üniversitesi Geriatrik Bilimler Araştırma Merkezi GEBAM, İ. Aygül Ofset. 2008.
13. Çekal N. Huzurevinde Kalan Yaşlıların Beslenme Servisi Örgütünden Memnuniyet Durumları. Aile ve Toplum Eğitim, Kültür ve Araştırma Dergisi, Temmuz-Ağustos-Eylül.2006; 43-53
14. American Dietetic Association. Practice paper of the American Dietetic Association: Individualized nutrition approaches for older adults in health care communities. (No: 110). Journal of the American Dietetic Association, October, 110, ABD: American Dietetic Association.2010.
15. Elsner RJF. Changes in eating behavior during the aging process. Eating Behaviors, Spring.2002;3(1), 15-43.
16. Oğlak S. Uzun Süreli Evde Bakım Hizmetleri ve Bakım Sigortası. Türk Geriatri Dergisi.2007; 10(2), 100-108.
17. Karaoğlu N, Karaoğlu MA. Özel Bir Hastanenin Dahiliye Polikliniğinde Yaşlı Hastalıkları İle İlgili Bir Çalışma. Türk Geriatri Dergisi.2009; 12(3), 130-137.
18. Gary PJ, Vellas BJ. Aging and nutrition. E. Ekhard ve L. J. Ziegler (Ed.). Present knowledge in nutrition. (s. 414-419). Washington DC: Filer ILSI Press.1996.
19. Kamp BJ, Wellman NS and Russell C. Position of the American Dietetic Association, American Society for Nutrition, and Society for Nutrition Education: Food and nutrition programs for community-residing older adults. (No: 2). Journal of Nutrition Education and Behavior. 2010; 42, 72-82.
20. Cuervo M, Ansorena D, Garcia A, Astiasaran I and Martinez JA. Food consumption analysis in Spanish elderly based upon Mini Nutritional Assessment Test. Annals of Nutrition and Metabolism.2008; 52, 299-307.
21. Rakıcıoğlu N. Yaşlılığın Beslenme Uzmanı Tarafından Değerlendirilmesi. S. Arioğul (Ed.). Geriatri ve Gerontoloji (s. 231-243). Ankara: MN & Nobel Basım. 2006.
22. Sanlier N and Yabancı N. Mini nutritional assessment in the elderly: Living alone, with family, a nursing home in Turkey. Nutrition & Food Science. 2006; 36(1), 50-58.
23. Sneed J and Strohbehn CH. Trends impacting food safety in retail foodservice: Implications for dietetics practice. Journal of the American Dietetic Association.2008; 108(7), 1170-1177.
24. Arslan P and Rakıcıoğlu N. Beslenme Risk Taraması ve Yaşlı Beslenmesi. Y. G. Kutsal (GEBAM) (Haz.). Yaşlılık Gerçeği. (s. 97-114). Ankara: Hacettepe Üniversitesi Hastaneleri Basımevi. 2004.
25. Tanyel E, Taşdelen FN, Tülek N, Leblebicioğlu H. Yaşlı Hastalardaki Üriner Sistem İnfeksiyonlarının Değerlendirilmesi. İnfeksiyon Dergisi. 2006; 20(2), 87-91.
26. Aksoydan E. Ankara'da Kendi Evinde ve Huzurevinde Yaşayan Yaşlıların Sağlık ve Beslenme Durumları. Türk Geriatri Dergisi.2006; 9(3), 150-157.
27. Oğuz MT. Yaşlılarda Görülen Biyolojik ve Sosyal Değişimler. Yüksek lisans tezi, Ankara Üniversitesi, Ankara. 2007.
28. Finkelstein JA and Schiffman SS. Workshop on taste and smell in the elderly: An overview. Physiology & Behavior.1999; 66(2), 173-176.
29. Türkiye İstatistik Kurumu. Sağlık Araştırması 2010 (Yayın No: 3654). Ankara: Türkiye İstatistik Kurumu. 2012.
30. Karaduman A, Yiğiter K, Aras Ö, Yakut Y. Yaşlılıkta Fiziksel Bağımsızlık ve Yaşam Kalitesi. Y. G. Kutsal (GEBAM) (Haz.). Yaşlılık Gerçeği. (s. 79-96). Ankara: Hacettepe Üniversitesi Hastaneleri Basımevi. 2004.

31. Özdemir G, ve Ersoy G. Yaşlanma Sürecinde Egzersiz ve Sağlıklı Beslenmenin Kazandırdıkları. Ankara: İlksan Matbaacılık. 2009.
32. Erdil F, Çelik ŞS. ve Baybuğa SM. Yaşlılık ve Hemşirelik Hizmetleri. Y. G. Kutsal (GEBAM) (Haz.). Yaşlılık Gerçeği. (s. 57-78). Ankara: Hacettepe Üniversitesi Hastaneleri Basımevi. 2004.
33. Sağlık Bakanlığı Temel Sağlık Hizmetleri Genel Müdürlüğü. Birinci Basamak Sağlık Hizmetlerinde Çalışan Hekimler İçin Yaşlı Sağlığı Tanı ve Tedavi Rehberi 2010 (Yayın No: 781). Ankara: Sağlık Bakanlığı. 2010.
34. Adolffson O, Meydani SN. Nutrition and the aging immune response. I. H. Rosenberg, A. Sastre (Ed.). Nutrition and aging. (s. 207-221). Nestle Nutrition Workshop Series Clinical & Performance Program, Nestle Nutrition Ltd. 2002.
35. Karaoğlu N, Karaoğlu MA. Özel Bir Hastanenin Dahiliye Polikliniğinde Yaşlı Hastalıkları İle İlgili Bir Çalışma. Türk Geriatri Dergisi. 2009; 12(3), 130-137.
36. Labossiere R, Bernard MA. Nutritional considerations in institutionalized elders. Current Opinion in Clinical Nutrition & Metabolic Care. 2008; 11, 1-6.
37. Cereda E. Mini nutritional assessment. Current Opinion in Clinical Nutrition & Metabolic Care. 2012; Jan-15(1), 29-41.
38. Mucci E, Jackson SHD. Nutritional supplementation in community-dwelling elderly people. Ann Nutr Metab 2008;52(Suppl 1):33-7.
39. Nutrition Screening Initiative. Nutrition statement of principle. Chicago: American Dietetic Institution and the American Academy of Family Physicians. 2002.
40. Arnaud-Battandier F, Malvy D, Jeandel C, et al. Use of oral supplements in malnourished elderly patients living in the community: a pharmaco-economic study. Clin Nutr. 2004;23(5):1096-103.
41. Johnson LE, Sullivan DE. Nutrition and failure to thrive. In: Landefeld CS, Palmer RM, Johnson MA, Johnston CB, Lyons WL, editors. Current geriatric treatment and diagnosis. International ed. New York: Mc Graw Hill Companies. 2004; 391-406.
42. Guigoz Y, Vellas B, Garry PJ. The Mini Nutritional Assessment (MNA): a practical assessment tool for grading the nutritional state of elderly patients. Facts and Research in Gerontology. 1994;4(Suppl 2):15-59
43. Johnson LE, Sullivan DE. Nutrition and failure to thrive. In: Landefeld CS, Palmer RM, Johnson MA, Johnston CB, Lyons WL, editors. Current geriatric treatment and diagnosis. International ed. New York: Mc Graw Hill Companies. 2004; 391-406.
44. DiMaria-Ghalili RA, Guenter PA. The mini nutritional assessment. Am J Nurs. 2008;108(2):50-9.
45. Akan H, Ayraller A, Hayran O. Evde sağlık birimine başvuran yaşlı hastaların beslenme durumları. Türk Aile Hek Derg. 2013;17(3):106-112.
46. Aydan Ç. Okcan B. Sema U. Evde Sağlık Hizmeti Alan Yaşlı Hastalarda Beslenme Durumunun Değerlendirilmesi ve Beslenme Durumunun Laboratuvar Parametreleri Üzerine Olan Etkisinin İrdelenmesi. Konuralp Tıp Dergisi. 2014;6(3):31-37.
47. Sibila RJ, Bruna PA, Anieli G, Schott M, Leonardo D, Andrea M, Elisângela C. Association of anemia and malnutrition in hospitalized patients with exclusive enteral nutrition. Nutr Hosp. 2018 Jun. 22;35(4):753-760. doi: 10.20960/nh.1628.
48. Matthews JH. Cobalamin and folate deficiency in the elderly. Baillères Clin Haematol. 1995; 54: 245-253.
49. Andrès E, Loukili NH, Noel E, et al. Vitamin B12 (cobalamin) deficiency in elderly patients. CMAJ 2004; 171: 251-259.
50. Saka B, Özkulluk H. İç hastalıkları polikliniğine başvuran yaşlı hastalarda nütrisyonel durumun değerlendirilmesi ve malnütrisyonun diğer geriatrik sendromlarla ilişkisi. Gülhane Tıp Dergisi. 2008; 50: 151-157.
51. Marton KI, Sox HC Jr, Krupp JR. Involuntary weight loss: diagnostic and prognostic significance. Ann Intern Med. 1981; 95: 568-574.
52. Sullivan DH, Patch GA, Walls RC, Lipschitz DA. Impact of nutrition status on morbidity and mortality in a select population of geriatric rehabilitation patients. Am J Clin Nutr. 1990; 51: 749-758.
53. Corish CA, Kennedy NP. Protein-energy undernutrition in hospital in-patients. Br J Nutr. 2000; 83: 575-591.
54. Visvanathan R. Under-nutrition in older people: a serious and growing global problem. J Postgrad Med. 2003; 49: 352-360.

Chapter 9

CLINICAL IMPORTANCE OF TOXIC METALS

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INTRODUCTION

Normal diet contains both essential and toxic metals. Aluminum, antimony, arsenic, berilium, cadmium, lead, mercury, nickel, platinum, silver, thalium and tin are the elements, which are known as toxic for humans. 1-5 Atomic numbers and weights (amu) of these elements are summarized in Table 1.

Table 1. Atomic numbers and atomic weights of toxic metals.

| Atomic | Al | Sb | As | Be | Cd | Pb | Hg | Ni | Pt | Ag | Tl | Sn |
|--------|----|-----|----|----|-----|-----|-----|----|-----|-----|-----|-----|
| Number | 13 | 51 | 33 | 4 | 48 | 82 | 80 | 28 | 78 | 47 | 81 | 50 |
| Weight | 27 | 122 | 75 | 9 | 112 | 207 | 201 | 59 | 195 | 108 | 204 | 119 |

Excessively high levels of physiologically essential elements such as iron, chromium, copper, manganese selenium also exhibit toxic effects. 1-5 In this chapter, brief information on the clinical importance of toxic metals will be given.

Aluminum (Al)

Healthy individuals are capable of excreting about 5-10 mg aluminum in a day through the kidneys. Dialysis is not an effective way to remove aluminum from the body. Therefore, some clinical problems such as dialysis encephalopathy or dementia may be observed in these patients. This metal may accumulate in the brain and provides a suitable environment for the development of amyloide plaques known as tau in Alzheimer's disease, which is a much more frequently observed neurodegenerative disease than ever in recent times. Since aluminum can replace calcium in bones, it may impair bone mineralization by simply incorporating itself into the structure of bone. Putting blood into the test tubes with rubber stopper for aluminum determination is the most frequently observed cause of contamination. Antacids also contain considerable amount of aluminum. Some

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interesting to note that some toxic elements are also being used during the treatment of severe diseases in the field of clinical medicine.

As the conclusive remarks, toxic elements listed with their characteristic features in this chapter deserve more attention due to environmental pollution. They are particularly important from the point of view of environmental medicine as well as occupational safety and health.

REFERENCES

1. Biesalski HK, Grimm P, Nowitzki-Grimm S. (2020). Georg Thieme Verlag, Stuttgart. Taschenatlas Ernährung
2. Donma MM, Donma O, Michalke B, Halbach S, Nischwitz V. (2012). Vitamins, Minerals and Metabolic Pathways in Health and Diseases with a Special Chapter on Speciation. Vitamins, Macrominerals, Electrolytes, Trace Elements and Toxic Metals. Istanbul, Turkey, Istanbul University Publishing House
3. Biesalski HK, Grimm P. (2004). Georg Thieme Verlag, Stuttgart. Taschenatlas der Ernährung
4. Moyer TP, Burritt MF, Butz J. (2006). Toxic Metals. In CA Burtis, ER Ashwood, DA Bruns, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 4th ed, St. Louis, Missouri, USA, Elsevier Saunders Inc.
5. Strathman FG, Blum L. (2018). Toxic elements. In Rifai N, Horvath AR and Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 6th ed. St. Louis, Missouri, USA, Elsevier Saunders Inc.
6. Igbokwe IO, Igwenagu E, Igbokwe NA. Aluminium toxicosis: a review of toxic actions and effects. *Interdiscip Toxicol.* 2019; 12(2):45-70.
7. Wang Y, Li H, Zhang J, et al. Effect of aluminum combined with ApoEε4 on Tau phosphorylation and Aβ deposition. *J Trace Elem Med Biol.* 2021; 64:126700.
8. Velasquez J, Wray AA. (2020). Deferoxamine. 2020 Dec 14. In: Stat Pearls (Int). Treasure Island (FL): Stat Pearls Publishing
9. Kumar S. Aluminum-induced changes in the rat brain serotonin system. *Food Chem Toxicol.* 2002; 40:1875-1880.
10. Ravi SM, Prabhu BM, Raju TR, et al. Long-term effects of postnatal aluminium exposure on acetylcholinesterase activity and biogenic amine neurotransmitters in rat brain. *Indian J Physiol Pharmacol.* 2000; 44: 473-478.
11. Yoshino M, Ito M, Haneda M, et al. Prooxidant action of aluminum ion-stimulation of iron-mediated lipid peroxidation by aluminum. *Biometals.* 1999; 12:237-40.
12. Hall NB, Halldin CN, Blackley DJ, et al. Assessment of pneumoconiosis in surface coal miners after implementation of a national radiographic surveillance program, 2014-2019, United States, *Am J Ind Med.* 2020; 63(12):1104-1108.
13. Cooper RG, Harrison AP. The exposure to and health effects of antimony. *Ind J Occup Environ Med.* 2009; 13(1): 3-10.
14. Filella M, Hennebert P, Okkenhaug G, et al. Occurrence and fate of antimony in plastics. *J Hazard Mater.* 2020; 390:121764.
15. Haldimann M, Blanc A, Dudler V. Exposure to antimony from polyethylene terephthalate (PET) trays used in ready-to-eat meals. *Food Addit Contam.* 2007; 24:860-8.
16. Haldimann M, Alt A, Blanc A, et al. Migration of antimony from PET trays into food simulants and food: determination of Arrhenius parameters and comparison of predicted and measured migration data. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess.* 2013; 30(3):587-598.
17. Chu J, Hu X, Kong L, et al. Dynamic flow and pollution of antimony from polyethylene terephthalate (PET) fibers in China. *Sci Total Environ.* 2021; 771:144643.

18. Allafi AR. The effect of temperature and storage time on the migration of antimony from polyethylene terephthalate (PET) into commercial bottled water in Kuwait. *Acta Biomed.* 2020; 91(4):e2020105.
19. Centers for Disease Control and Prevention (CDC). Pseudo-outbreak of antimony toxicity in firefighters - Florida, 2009. *MMWR Morb Mortal Wkly Rep.* 2009; 58:1300-1302.
20. de Perio MA, Durgam S, Caldwell KL, et al. A health hazard evaluation of antimony exposure in fire fighters. *J Occup Environ Med.* 2010; 52:81-84.
21. Bozack AK, Saxena R, Gamble MV. Nutritional influences on one-carbon metabolism: Effects on arsenic methylation and toxicity. *Annu Rev Nutr.* 2018; 38:401-429.
22. Dubey M, Shea TB. Potentiation of arsenic neurotoxicity by folate deprivation: Protective role of S-adenosyl methionine. *Nutr Neurosci.* 2007; 10:199-204.
23. Gamble MV, Liu X, Slavkovich V, et al. Folic acid supplementation lowers blood arsenic. *Am J Clin Nutr.* 2007; 86:1202-1209.
24. Tseng CH. A review on environmental factors regulating arsenic methylation in humans. *Toxicol Appl Pharmacol.* 2009; 235:338-350.
25. Lievrement D, Bertin PN, Lett MC. Arsenic in contaminated waters: Biogeochemical cycle, microbial metabolism and biotreatment processes. *Biochimie.* 2009; 91:1229-1237.
26. Masoti A, Da Sacco L, Bottazzo GF, et al. Risk assessment of inorganic arsenic pollution on human health. *Environ Pollut.* 2009; 157:1771-1772.
27. Ahmad S, Kitchin KT, Cullen WR. Arsenic species that cause release of iron from ferritin and generation of activated oxygen. *Arch Biochem Biophys.* 2000; 382:195-202.
28. Chen Y, Parvez F, Gamble M, et al. Arsenic exposure at low to moderate levels and skin lesions, arsenic metabolism, neurological functions, and biomarkers for respiratory and cardiovascular diseases. *Toxicol Appl Pharmacol.* 2009; 239:184-192.
29. Zierold KM, Knobloch L, Anderson H. Prevalence of chronic diseases in adults exposed to arsenic-contaminated drinking water. *Am J Public Health.* 2004; 94:1936-1937.
30. Smeester L, Fry RC. Long-term health effects and underlying biological mechanisms of developmental exposure to arsenic. *Curr Environ Health Rep.* 2018; 5(1):134-144.
31. Occupational Safety and Health Administration (OSHA), Department of Labor. Occupational Exposure to Beryllium. Final rule. *Fed Regist.* 2017; 82(5):2470-2757.
32. Hollins DM, McKinley MA, Williams C, et al. Beryllium and lung cancer: a weight of evidence evaluation of the toxicological and epidemiological literature. *Crit Rev Toxicol.* 2009; 39:1-32.
33. Deubner DC, Roth HD. Rejoinder: Progress in understanding the relationship between beryllium exposure and lung cancer. *Epidemiology.* 2009; 20:341-343.
34. Balmes JR, Abraham JL, Dweik RA, et al. An official American Thoracic Society statement: diagnosis and management of beryllium sensitivity and chronic beryllium disease. *Am J Respir Crit Care Med.* 2014; 190(10):e34-59.
35. Cummings KJ, Stefaniak AB, Virji MA, et al. A reconsideration of acute beryllium disease. *Environ Health Perspect.* 2009; 117:1250-1256.
36. MacMurdo MG, Mroz MM, Culver DA, et al. Chronic beryllium disease: Update on a moving target. *Chest.* 2020; 158(6):2458-2466.
37. Satarug S, Garrett SH, Sens MA, et al. Cadmium, environmental exposure and health outcomes. *Environ Health Perspect.* 2010; 118: 182-190.
38. Donma O, Donma MM. Cadmium, lead and phytochemicals. *Med Hypotheses.* 2005; 65: 699-702.
39. https://www.who.int/ipcs/assessment/public_health/cadmium/en/
40. <https://www.osha.gov/cadmium>
41. <https://www.atsdr.cdc.gov/>
42. Richter PA, Bishop EE, Wang JT, et al. Tobacco smoke exposure and levels of urinary metals in the US youth and adult population: The national health and nutrition examination survey (NHANES) 1999-2004. *Int J Environ Res Public Health.* 2009; 6:1930-1946.
43. Genchi G, Sinicropi MS, Lauria G, et al. The effects of cadmium toxicity. *Int J Environ Res Pub-*

- lic Health.* 2020; 17(11):3782.
44. Olsson IM, Bensryd I, Lundh T, et al. Cadmium in blood and urine. Impact of sex, age, dietary intake, iron status, and former smoking. Association of renal effects. *Environ Health Perspect.* 2002; 110:1185-1190.
 45. Baye H, Hymete A. Lead and cadmium accumulation in medicinal plants collected from environmentally different sites. *Bull Environ Contam Toxicol.* 2010; 84:197-201.
 46. Joseph P. Mechanisms of cadmium carcinogenesis. *Toxicol Appl Pharmacol.* 2009; 238:272-279.
 47. Ebrahimi M, Khalili N, Razi S, et al. Effects of lead and cadmium on the immune system and cancer progression. *J Environ Health Sci Eng.* 2020; 18(1):335-343.
 48. Kshirsagar MS, Patil JA, Patil A. Increased blood lead level induces oxidative stress and alters the antioxidant status of spray painters. *J Basic Clin Physiol Pharmacol.* 2020; 31(2)
 49. Kasuba V, Rozgaj R, Milić M, et al. Evaluation of lead exposure in battery-manufacturing workers with focus on different biomarkers. *J Appl Toxicol.* 2010; 30(4):321-8.
 50. Liu Y, McDermott S, Lawson A, et al. The relationship between mental retardation and developmental delays in children and the levels of arsenic, mercury and lead in soil samples taken near their mother's residence during pregnancy. *Int J Hyg Environ Health.* 2010; 213:116-23.
 51. Rhodes D, Spiro A, Aro A, et al. Relationship of bone and blood lead levels to psychiatric symptoms: the normative aging study. *J Occup Environ Med.* 2003; 45: 1144-51.
 52. Koshy B, Srinivasan M, Zachariah SM, et al. Body iron and lead status in early childhood and its effects on development and cognition: a longitudinal study from urban Vellore. *Public Health Nutr.* 2020; 23(11):1896-1906.
 53. Prasanthi RP, Devi CB, Basha DC, et al. Calcium and zinc supplementation protects lead (Pb)-induced perturbations in antioxidant enzymes and lipid peroxidation in developing mouse brain. *Int J Dev Neurosci.* 2010; 28:161-7.
 54. Gidlow DA. Lead toxicity. *Occup Med (Lond).* 2015;65(5):348-56.
 55. Counter SA, Buchanan LH, Ortega F. Neurophysiologic and neurocognitive case profiles of Andean patients with chronic environmental lead poisoning. *J Toxicol Environ Health A.* 2009; 72:1150-9.
 56. Eastman KL, Tortora LE. Lead Encephalopathy. (2020). In: StatPearls (Internet). Treasure Island (FL): Stat Pearls Publishing
 57. Eiró LG, Ferreira MKM, Bittencourt LO, et al. Chronic methylmercury exposure causes spinal cord impairment: Proteomic modulation and oxidative stress. *Food Chem Toxicol.* 2020; 146:111772.
 58. Ceccatelli S, Daré E, Moors M. Methylmercury-induced neurotoxicity and apoptosis. *Chem Biol Interact.* 2010; 188:301-308.
 59. Liao Y, Peng S, He L, et al. Methylmercury cytotoxicity and possible mechanisms in human trophoblastic HTR-8/SVneo cells. *Ecotoxicol Environ Saf.* 2021;207:111520.
 60. Kimáková T, Kuzmová L, Nevolná Z, Bencko V. Fish and fish products as risk factors of mercury exposure. *Ann Agric Environ Med.* 2018; 25(3):488-493.
 61. Du B, Yin R, Fu X, et al. Use of mercury isotopes to quantify sources of human inorganic mercury exposure and metabolic processes in the human body. *Environ Int.* 2021; 147:106336.
 62. Santos-Sacramento L, Arrifano GP, Lopes-Araújo A, et al. Human neurotoxicity of mercury in the Amazon: A scoping review with insights and critical considerations. *Ecotoxicol Environ Saf.* 2021; 208:111686.
 63. Gump BB, Dykas MJ, MacKenzie JA, et al. Background lead and mercury exposures: Psychological and behavioral problems in children. *Environ Res.* 2017; 158:576-582.
 64. Bridges CC, Zalups RK. The aging kidney and the nephrotoxic effects of mercury. *J Toxicol Environ Health B Crit Rev.* 2017; 20(2):55-80.
 65. Shenker BJ, Guo TL, Insug O, et al. Induction of apoptosis in human T-cells by methyl mercury: temporal relationship between mitochondrial dysfunction and loss of reductive reserve. *Toxicol Appl Pharmacol* 1999; 157:23-35.
 66. Genchi G, Carocci A, Lauria G, et al. Nickel: Human health and environmental toxicology. *Int*

- J Environ Res Public Health*. 2020; 17(3):679.
67. Donma MM, Donma O. Arsenic and Nickel: Unavoidable constituents of our everyday diet. *Med Hypotheses*. 2006; 66:681.
 68. Rusin D, Nickeson D, Tustin AW. A fatal workplace nickel carbonyl exposure. *Clin Toxicol (Phila)*. 2019; 57(1):63-64.
 69. Divya VC, Karthikeyan BS. Enhanced nickel sensitivity in iron deficiency anemia. *Indian J Public Health*. 2017; 61(3):215.
 70. Rishor-Olney CR, Gnugnoli DM. Nickel Allergy. (2020). In: Stat Pearls (Int). Treasure Island (FL): Stat Pearls Publishing
 71. Kawanishi S, Inoue S, Oikawa S, et al. Oxidative DNA damage in cultured cells and rat lungs by carcinogenic nickel compounds. *Free Radic Biol Med*. 2001; 31:108-116.
 72. Wang L, Sun C, Li X, et al. A pharmacogenetics study of platinum-based chemotherapy in lung cancer: ABCG2 polymorphism and its genetic interaction with SLC31A1 are associated with response and survival. *J Cancer*. 2021; 12(5):1270-1283.
 73. <https://www.fda.gov/medical-devices/breast-implants/fda-back-grounder-platinum-silicone-breast-implants>. (Content current as of:01/18/2018)
 74. Ueda Y, Enokida T, Okano S, et al. Combination treatment with Paclitaxel, Carboplatin, and Cetuximab (PCE) as first-line treatment in patients with recurrent and/or metastatic nasopharyngeal carcinoma. *Front Oncol*. 2020; 10:571304.
 75. Zhang M, Iv CTH, Foley H, et al. Co-delivery of etoposide and cisplatin in dual drug loaded nanoparticles synergistically improves chemoradiotherapy in non-small cell lung cancer models. *Acta Biomater*. 2021; S1742-7061(21)00086-6.
 76. Chen X, Hong Y, Feng J, et al. Concurrent chemoradiotherapy comparison of taxanes and platinum versus 5-fluorouracil and platinum in nasopharyngeal carcinoma treatment. *Chin Med J (Engl)*. 2014; 127(1):142-149.
 77. Manohar S, Leung N. Cisplatin nephrotoxicity: a review of the literature. *J Nephrol*. 2018; 31:15-25.
 78. Lara HH, Ayala-Nunez NV, Turrent LDI, et al. Bactericidal effect of silver nanoparticles against multidrug-resistant bacteria. *World J Microbiol Biotechnol*. 2010; 615-621.
 79. Ferreira LAB, Dos Reis SB, do Nascimento da Silva E, et al. Thiol-antioxidants interfere with assessing silver nanoparticle cytotoxicity. *Nanomedicine*. 2020; 24:102130.
 80. Drake PL, Hazelwood KJ. Exposure-related health effects of silver and silver compounds: A review. *Annals Occup Hygiene*. 2005; 49:575-585.
 81. Hadrup N, Sharma AK, Loeschner K, et al. Pulmonary toxicity of silver vapours, nanoparticles and fine dusts: A review. *Regul Toxicol Pharmacol*. 2020; 115:104690.
 82. Fisher NM, Marsh E, Lazova R. Scar-localized argyria secondary to silver sulfadiazine cream. *J Am Acad Dermatol*. 2003; 49:730-732.
 83. Forycki Z, Zegarski W, Bardzik J et al. Acute silver poisoning through inhalation. *Bull Inst Marit Trop Med Gdynia*. 1983; 34: 199-203.
 84. Sanchez-Huerta V, DeWit-Carter G, Hernandez-Quintela E, et al. Occupational corneal argyrosis in art silver solderers. *Cornea*. 2003; 22: 604-611.
 85. Pavlíková J, Zbírál J, Smatanová M, et al. Uptake of thallium from naturally-contaminated soils into vegetables. *Food Addit Contam*. 2006; 23:484-491.
 86. Montes S, Soriano L, Ríos C, et al. Endogenous thiols enhance thallium toxicity. *Arch Toxicol*. 2007; 81:683-687.
 87. Kuo HC, Huang CC, Tsai YT, et al. Acute painful neuropathy in thallium poisoning. *Neurology*. 2005; 65:302-304.
 88. Peter AL, Viraraghavan T. Thallium: a review of public health and environmental concerns. *Environ Int*. 2005; 31:493-501.
 89. Sharma AN, Nelson LS, Hoffman RS. Cerebrospinal fluid analysis in fatal thallium poisoning: evidence for delayed distribution into the central nervous system. *Am J Forensic Med Pathol*. 2004; 25:156-158.

90. Tsai YT, Huang CC, Kuo HC, et al. Central nervous system effects in acute thallium poisoning. *Neurotoxicology*. 2006; 27:291-295.
91. Zhang HT, Qiao BP, Liu BP, et al. Study on the treatment of acute thallium poisoning. *Am J Med Sci*. 2014; 347(5):377-381.
92. Wu M, Wang L, Song L, et al. The association between prenatal exposure to thallium and shortened telomere length of newborns. *Chemosphere*. 2021 ;265:129025.
93. Yang HR, Kim ES, Ko YS, et al. Food intake survey of kindergarten children in Korea: Part 2 increased dietary intake of tin possibly associated with canned foods. *Environ Health Prev Med*. 2015; 20(4):302-306.
94. Deshwal GK, Panjagari NR. Review on metal packaging: materials, forms, food applications, safety and recyclability. *J Food Sci Technol*. 2020; 57(7):2377-2392.
95. <https://www.atsdr.cdc.gov>
96. Gerasimchuk N, Maher T, Durham P, et al. Tin(IV) cyanoximates: synthesis, characterization, and cytotoxicity. *Inorg Chem*. 2007; 46:7268-7284.
97. Milaeva E, Petrosyan V, Berberova N, et al. Organic derivatives of mercury and tin as promoters of membrane lipid peroxidation. *Bioinorg Chem Appl*. 2004; 2(1-2):69-91.
98. Jones SR, Atkin P, Holroyd C, et al. Lung cancer mortality at a UK tin smelter. *Occup Med (Lond)*. 2007; 57:238-245.
99. Nguyen TT, Föllner M, Lang F. Tin triggers suicidal death of erythrocytes. *J Appl Toxicol*. 2009; 29:79-83.
100. van Loveren C, Gerardu VA, Sissons CH, et al. Effect of various rinsing protocols after use of amine fluoride/stannous fluoride toothpaste on the bacterial composition of dental plaque. *Caries Res*. 2009; 43:462-467.
101. Day T, Einwag J, Hermann JS, et al. A clinical assessment of the efficacy of a stannous-containing sodium fluoride dentifrice on dentinal hypersensitivity. *J Contemp Dent Pract*. 2010; 11:E001-8.

Chapter 10

PHYTOCHEMICALS AND CHRONIC DISEASES

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INTRODUCTION

Phytochemicals are biologically active compounds in plants. Their antioxidant properties have drawn attention in recent years. Epidemiological studies indicate that there is a clear association between increased consumption of fruits/vegetables and decreased incidences of cardiovascular diseases as well as most of the cancers due to phytochemicals in them. Phytochemicals also control hypertension and diabetes. They also play roles in the management of metabolic syndrome. It is reported that cherries cause significant reductions in the elevated uric acid levels observed in gout disease. They also exert beneficial effects on some infectious agents. Therefore, consumption of fruits/vegetables five times a day is recommended for optimal phytochemical intake. About 1-1.5 g of phytochemicals per day should be included into the diet. Vegetarian type of nutrition is associated with significantly high intake of phytochemicals. (1-12)

Classification of Phytochemicals

Phytochemicals are classified depending on their basic structural features:

All **polyphenols** possess the same basic phenolic structure. Resveratrol, epigallocatechin gallate, quercetin, genistein, curcumin, ellagic acid are very important phytochemicals possessing polyphenolic structure. They are generally found in foods such as green tea, bitter chocolate, turmeric, berries, red grapes, cherries, apple, soy bean. Flavonoids constitute the largest polyphenol group. Aside from phenolic acids such as flavonoids, ellagic acid, phytoestrogens covering stilbenes like resveratrol, lignans, comestan and isoflavonoids are also included in this group. Such compounds also known as isoflavons exhibit effects similar to those of female sex hormone estrogens. Flavonoids are known as protective molecules fighting against free oxygen radicals and other reactive oxygen species, which are responsible for the progression of aging and the development of many diseases. Curcumin, being the most studied polyphenol, possesses health beneficial effects

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protective potential against aging. Antioxidant phytochemicals such as epigallocatechin gallate, allicin, curcumin, resveratrol, proanthocyanidins are the molecules, which increase life-span, relieve cognitive function disorders, ameliorate the age-dependent inflammation and oxidative stress. (88-93)

Alzheimer's disease is a progressive neurodegenerative disease characterized by memory loss. Symptoms have tendency to develop slowly and gradually worsen over time. Brain is particularly sensitive to oxidative stress caused by the elevated levels of oxygen radicals. Since acetylcholin levels are significantly reduced in these patients, inhibiting acetylcholinesterase activity may be effective to relieve symptoms. Therefore, phytochemicals with oxidative stress- and acetylcholinesterase activity- reducing capacity will be protective in fighting against Alzheimer's disease. It was reported that curcumin, catechins and resveratrol have neuroprotective effects. Since polyphenols in walnut decrease oxidants as well as inflammatory burden in brain cells, they may play roles in the prevention of this disease. (94-97)

CONCLUSION

Phytochemicals can be considered as the very recent class of micronutrients after vitamins and minerals. 98 Dietary phytochemicals alter redox status. They act as repressive or blocking agents in cancer initiation or progression steps by binding proteins or by modulating functions of enzymes such as kinases. In spite of the fact that phytochemicals are proved to possess many health beneficial effects, clinical utility of dietary phytochemicals is limited because their concentrations in blood are too low to be detected.

Due to their lipophilic properties, their low absorptivity as well as solubility in an aqueous environment and high conversion rate to their metabolites are among the other reasons preventing the maximum benefit of them.

Recent technologies 99 such as the use of nanocarriers, incorporation into proteins and lipids, coating with essential natural oils, or the use of synthetic analogues are being used to increase bioefficacy of phytochemicals.

REFERENCES

1. Guan R, Van Le Q, Yang H, et al. A review of dietary phytochemicals and their relation to oxidative stress and human diseases. *Chemosphere*. 2021;271:129499.
2. Donma MM, Donma O. The effects of allium sativum on immunity within the scope of COVID-19 infection. *Med Hypotheses*. 2020;144:109934.
3. Biesalski HK, Grimm P, Nowitzki-Grimm S. (2020). Georg Thieme Verlag, Stuttgart, Taschenatlas Ernährung
4. Pop RM, Popolo A, Trifa AP, et al. Phytochemicals in cardiovascular and respiratory diseases: Evidence in oxidative stress and inflammation. *Oxid Med Cell Longev*. 2018; 2018:1603872.

5. Biesalski HK, Grimm P. (2004). Georg Thieme Verlag, Stuttgart, Taschenatlas der Ernährung
6. Zhang YJ, Gan RY, Li S, et al. Antioxidant phytochemicals for the prevention and treatment of chronic diseases. *Molecules* 2015; 20: 21138-21156.
7. Aghajanjpour M, Nazer MR, Obeidavi Z, et al. Functional foods and their role in cancer prevention and health promotion: a comprehensive review. *Am J Cancer Res.* 2017; 7(4):740-769.
8. Park HA. Fruit intake to prevent and control hypertension and diabetes. *Korean J Fam Med.* 2021; 42(1):9-16.
9. Cicero AFG, Colletti A. Role of phytochemicals in the management of metabolic syndrome. *Phytomedicine.* 2016; 23(11):1134-1144.
10. Collins MW, Saag KG, Singh JA. Is there a role for cherries in the management of gout? *Ther Adv Musculoskelet Dis.* 2019; 11: 1759720X19847018.
11. Donma O, Donma MM, Sonmez S. Metal speciation, phytochemicals and Helicobacter pylori infection. *Med Hypotheses.* 2006; 67: 545-549.
12. Chojnacka K, Witek-Krowiak A, Skrzypczak D, et al. Phytochemicals containing biologically active polyphenols as an effective agent against Covid-19-inducing coronavirus. *J Func Foods.* 2020; 73: 104146.
13. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. *Oxid Med Cell Longev.* 2009; 2(5):270-8.
14. 14: Cory H, Passarelli S, Szeto J, et al. The role of polyphenols in human health and food systems: A mini-review. *Front Nutr.* 2018; 5:87.
15. Mrduljaš N, Krešić G, Bilušić T. Polyphenols: Food Sources and Health Benefits, Functional Food - Improve Health through Adequate Food, Maria Chavarri Hueda, Intech Open, (Aug, 2017) DOI: 10.5772/ intechopen.68862. Available from: <https://www.intechopen.com/books/functional-food-improve-health-through-adequate-food/polyphenols-food-sources-and-health-benefits>
16. Rasouli H, Farzaei MH, Khodarahmi R. Polyphenols and their benefits: A review. *Int J Food Propert.* 2017; 20(sup2), 1700-1741.
17. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. *J Nutr Sci.* 2016; 5:e47.
18. Mozaffarian D, Wu JHY. Flavonoids, dairy foods, and cardiovascular and metabolic health. A review of emerging biologic pathways. *Circ Res.* 2018; 122:369-384.
19. Speirs V. (2011). Phytoestrogens. In: Schwab M. (eds). Springer, Berlin, Heidelberg..Encyclopedia of Cancer
20. Torrens-Mas M, Roca P. Phytoestrogens for cancer prevention and treatment. *Biology.* 2020; 9(12):427.
21. Cady N, Peterson SR, Freedman SN, et al. Beyond metabolism: The complex interplay between dietary phytoestrogens, gut bacteria, and cells of nervous and immune systems. *Front Neurol.* 2020; 11:150.
22. Maoka T. Carotenoids as natural functional pigments. *J Nat Med.* 2020; 74: 1–16.
23. Górecka D, Wawrzyniak A, Jędrusek-Golińska A, et al. Lycopene in tomatoes and tomato products. *Open Chem.* 2020; 18: 752–756.
24. Kumar VNP, Elango P, Asmathulla S, et al. A systematic review on lycopene and its beneficial effects. *Biomed Pharmacol J.* 2017; 10(4): 2113-2120.
25. Mozos I, Stoian D, Caraba A, et al. Lycopene and vascular health. *Front. Pharmacol.* 2018; 9:521.
26. Thomas SE, Johnson EJ. Xanthophylls. *Adv Nutr.* 2018; 9(2): 160–162.
27. Buscemi S, Corleo D, Di Pace F, et al. The effect of lutein on eye and extra-eye health. *Nutrients.* 2018; 10(9):1321.

28. Perrone S, Tei M, Longini M, et al. The multiple facets of lutein: A call for further investigation in the perinatal period. *Oxidative Med Cellular Longevity*. 2016; 2016: Article ID 5381540.
29. Stringham JM, Johnson EJ, Hammond BR. Lutein across the lifespan: From childhood cognitive performance to the aging eye and brain. *Curr Dev Nutr*. 2019; 3(7): nzz066.
30. Burri BJ, La Frano MR, Zhu C. Absorption, metabolism, and functions of β -cryptoxanthin. *Nutr Rev*. 2016; 74(2):69-82.
31. Burri BJ. Beta-cryptoxanthin as a source of vitamin A. *J Sci Food Agric*. 2015; 95(9):1786-1794.
32. Jiao Y, Reuss L, Wang Y. β -Cryptoxanthin: Chemistry, occurrence, and potential health benefits. *Curr Pharmacol Rep*. 2019; 5: 20–34.
33. Olmedilla-Alonso B, Rodríguez-Rodríguez E, Beltrán-de-Miguel B, et al. Dietary β -cryptoxanthin and α -carotene have greater apparent bioavailability than β -carotene in subjects from countries with different dietary patterns. *Nutrients*. 2020; 12(9):2639.
34. Murillo AG, Hu S, Fernandez ML. Zeaxanthin: Metabolism, properties, and antioxidant protection of eyes, heart, liver, and skin. *Antioxidants Basel*. 2019; 8(9):390.
35. Obana A, Gohto Y, Nakazawa R, et al. Effect of an antioxidant supplement containing high dose lutein and zeaxanthin on macular pigment and skin carotenoid levels. *Sci Rep*. 2020; 10, 10262.
36. Raman G, Haslam D, Avendano E, et al. Lutein/zeaxanthin intake and visual outcomes in adults with healthy eyes: Qualitative gap analysis. *Cogent Med*. 2019; 6:1, 1683939
37. Mares J. Lutein and zeaxanthin isomers in eye health and disease. *Ann Rev Nutr*. 2016; 36(1):571-602.
38. Barba FJ, Nikmaram N, Roohinejad S, et al. Bioavailability of glucosinolates and their breakdown products: Impact of processing. *Front. Nutr*. 2016; 3:24.
39. Melrose J. The glucosinolates: A sulphur glucoside family of mustard anti-tumour and antimicrobial phytochemicals of potential therapeutic application. *Biomedicines*. 2019; 7(3):62.
40. Wu X, Zhou QH, Xu K. Are isothiocyanates potential anti-cancer drugs?. *Acta Pharmacol Sin*. 2009; 30(5):501-512.
41. Esteve M. Mechanisms underlying biological effects of cruciferous glucosinolate-derived isothiocyanates/indoles: A focus on metabolic syndrome. *Front. Nutr*. 2020; 7:111.
42. Kozioł A, Stryjewska A, Librowski T, et al. An Overview of the pharmacological properties and potential applications of natural monoterpenes. *Mini Rev Med Chem*. 2014; 14: 1156-1168
43. Wojtunik-Kulesza KA, Kasprzak K, Oniszczuk T, et al. Natural monoterpenes: Much more than only a scent. *C&B*. 2019; 16: e1900434.
44. Rogowska A, Szakiel A. The role of sterols in plant response to abiotic stress. *Phytochem Rev*. 2020; 19: 1525–1538.
45. Aboobucker SI, Suza WP. Why do plants convert sitosterol to stigmasterol? *Front. Plant Sci*. 2019; 10:354.
46. Ras R, Geleijnse J, Trautwein E. LDL-cholesterol-lowering effect of plant sterols and stanols across different dose ranges: A meta-analysis of randomised controlled studies. *Br J Nutr*. 2014; 112(2): 214-219.
47. Ruhee RT, Roberts LA, Ma S, et al. Organosulfur compounds: A review of their anti-inflammatory effects in human health. *Front Nutr*. 2020; 7:64.
48. Walag AMP. (2020). Health Benefits of Organosulfur Compounds. In: Egbuna C., Dable Tupas G. (eds) *Functional Foods and Nutraceuticals*. Cham. Springer
49. Miekus N, Marszałek K, Podlacha M, et al. Health benefits of plant-derived sulfur compounds, glucosinolates, and organosulfur compounds. *Molecules*. 2020; 25: 3804.
50. Singh B, Singh JP, Kaur A, et al. Bioactive compounds in banana and their associated health benefits. *Food Chem*. 2016; 206: 1-11.
51. Donma MM, Donma O. Phytonutrients and children: The other side of the medallion. *Food Res. Int*. 2005; 38(6) : 681-692.
52. Donma O, Donma MM. Cadmium, lead and phytochemicals. *Med Hypotheses*. 2005; 65: 699-702.

53. Durenne B, Druart P, Blondel A, et al. How cadmium affects the fitness and the glucosinolate content of oilseed rape plantlets. *Environ Exp Botany*. 2018; 155: 185-194.
54. Donma MM, Donma O. Arsenic and nickel: Unavoidable constituents of our everyday diet. *Med Hypotheses*. 2006; 66: 681.
55. Gupta RK, Gangoliya SS, Singh NK. Reduction of phytic acid and enhancement of bioavailable micronutrients in food grains. *J Food Sci Technol*. 2015; 52(2):676-684.
56. Middha P, Weinstein SJ, Männistö S, et al. β -Carotene supplementation and lung cancer incidence in the alpha-tocopherol, beta-carotene cancer prevention study: The role of tar and nicotine. *Nicotine Tob Res*. 2019; 21(8):1045-1050.
57. Eghbaliferiz S, Iranshahi M. Prooxidant activity of polyphenols, flavonoids, anthocyanins and carotenoids: Updated review of mechanisms and catalyzing metals. *Phytother Res*. 2016; 30(9):1379-1391.
58. Pildain MB, Vaamonde G, Cabral D. Analysis of population structure of *Aspergillus flavus* from peanut based on vegetative compatibility, geographic origin, mycotoxin and sclerotia production. *Int J Food Microbiol*. 2004; 93:31-40.
59. Donma MM, Donma O. Phytochemical supplementation of breast milk against mycotoxin contamination and childhood obesity. *Int J Ped Obes*. 2009; 3(2); 39.
60. Koszucka A, Nowak A, Nowak I, et al. Acrylamide in human diet, its metabolism, toxicity, inactivation and the associated European Union legal regulations in food industry. *Crit Rev Food Sci Nutr*. 2020; 60(10):1677-1692.
61. Liu H, Roasa J, Mats L, et al. (2020). Effect of acid on glycoalkaloids and acrylamide in French fries. *Food Additives & Contaminants: Part A* 37:6, 938-945
62. Amer FS, Reddivari L, Madiwale GP, et al. Effect of genotype and storage on glycoalkaloid and acrylamide content and sensory attributes of potato chips. *Am J Potato Res*. 2014; 91(6), 632-641.
63. Assayed ME, Abd El-Aty AM. Cruciferous plants: phytochemical toxicity versus cancer chemoprotection. *Mini Rev Med Chem*. 2009; 9(13):1470-1478.
64. Higdon JV, Delage B, Williams DE, et al. Cruciferous vegetables and human cancer risk: epidemiologic evidence and mechanistic basis. *Pharmacol Res*. 2007; 55(3):224-236.
65. Butt M, Sultan MT. Selected functional foods for potential in disease treatment and their regulatory issues. *Int J Food Properties*. 2013; 16(2): 397-415.
66. Pagliaro B, Santolamazza C, Simonelli F, et al. Phytochemical Compounds and Protection from Cardiovascular Diseases: A State of the Art. *BioMed Res Int*. 2015; 2015: Article ID 918069.
67. Donma MM, Donma O. (2020). Functional Foods for Obesity Management. In General Internal Medicine, Ed. AK Kadiroglu, Ch.2, pp. 9-19, AYBAK, Ankara, Turkey, Akademisyen Publishing House
68. Majeed M, Majeed S, Nagabhusanam K, et al. Lesser investigated natural ingredients for the management of obesity. *Nutrients*. 2021; 13(2):510.
69. Sunkara R, Verghese M. Functional foods for obesity management. *Food Nutr Sci*. 2014; 5: 1359-1369.
70. Myrie SB, Jones PJH. (2011). Functional foods and obesity, Editor(s): Maria Saarela, In Woodhead Publishing Series in Food Science, Technology and Nutrition, Functional Foods (Second Edition), pp: 234-260, Woodhead Publishing
71. Tingirikari JMR. Functional foods for treatment and prevention of obesity and its associated disorders. *Nutraceutical and Functional Foods in Disease Prevention*. 2019; 93-124. <http://doi:10.4018/978-1-5225-3267-5.ch004>
72. Lindström J, Virtanen SM. (2011). Functional foods and prevention of diabetes, Editor(s): Maria Saarela, In Woodhead Publishing Series in Food Science, Technology and Nutrition, Functional Foods (Second Edition), pp:261-276, Woodhead Publishing
73. Alkhatib A, Tsang C, Tiss A, et al. Functional foods and lifestyle approaches for diabetes prevention and management. *Nutrients*. 2017; 9(12):1310.

74. Mirmiran P, Bahadoran Z, Azizi F. Functional foods-based diet as a novel dietary approach for management of type 2 diabetes and its complications: A review. *World J Diabetes*. 2014; 5(3):267-281.
75. Gabriele R, Brunella C, Olga V. (2011). Functional Foods for Diabetes and Obesity. In book: Nutritional and Metabolic Bases of Cardiovascular Disease (pp.138-146) <http://doi:10.1002/9781444318456.ch18>
76. Hamasaki H. Functional foods for type 2 diabetes. *AIMS Med Sci*. 2016; 3(3): 278-297.
77. Giacco R, Giulio B, Vitale M, et al. Functional foods: Can food technology help in the prevention and treatment of diabetes? *Food Nutr Sci*. 2013; 4(8) 827-837.
78. Donma O, Donma MM. Dietary metals, phytochemicals and cancer. *J Nutr*. 2003; 133: 3866S.
79. Maru GB, Hudlikar RR, Kumar G, et al. Understanding the molecular mechanisms of cancer prevention by dietary phytochemicals. From experimental models to clinical trials. *World J Biol Chem*. 2016; 7(1):88-99.
80. Surh YJ. Cancer chemoprevention with dietary phytochemicals. *Nature Rev Cancer*. 2003; 3: 768-780.
81. Bhaskara VK, Mittal B, Mysorekar VV, et al. Resveratrol, cancer and cancer stem cells: A review on past to future. *Curr Res Food Sci*. 2020; 3:284-295.
82. Li F, Qasim S, Li D, et al. Updated review on green tea polyphenol epigallocatechin-3-gallate as a cancer epigenetic regulator. *Semin Cancer Biol*. 2021: S1044-579X(20)30256-X.
83. Islam SMR, Siddiqua TJ. (2020). Functional foods in cancer prevention and therapy: Recent epidemiological findings, Editor(s): Yearul Kabir, Functional Foods in Cancer Prevention and Therapy, pp:405-433, Academic Press
84. Shin DW, Lim BO. Nutritional interventions using functional foods and nutraceuticals to improve inflammatory bowel disease. *J Med Food*. 2020; 23(11):1136-1145.
85. Mijan MA, Lim BO. Diets, functional foods, and nutraceuticals as alternative therapies for inflammatory bowel disease: Present status and future trends. *World J Gastroenterol*. 2018; 24(25):2673-2685.
86. Singharaj B, Castaneda L, Riscuta G, et al. Functional foods, conventional treatment and bioactive compounds, assist in management of inflammatory bowel disease. *Bioactive Comp Health Dis*. 2018; 1(4); 40-59.
87. Uranga JA, López-Miranda V, Lombó F, et al. Food, nutrients and nutraceuticals affecting the course of inflammatory bowel disease. *Pharmacol Rep*. 2016; 68(4): 816-826.
88. Singh P, Sivanandam TM, Konar A, et al. Role of nutraceuticals in cognition during aging and related disorders. *Neurochem Int*. 2021; 143:104928.
89. Cho S. The role of functional foods in cutaneous anti-aging. *J Lifestyle Med*. 2014; 4(1):8-16.
90. Huhn SA, Witte V. (2017). Effects of Resveratrol on Cognitive Functions, Editor(s): Ronald Ross Watson, Nutrition and Functional Foods for Healthy Aging, Chapter 24, pp: 283-292, Academic Press
91. Martinez KB, Mackert JD, Michael MK. (2017). Polyphenols and Intestinal Health, Editor(s): Ronald Ross Watson, Nutrition and Functional Foods for Healthy Aging, Chapter 18, pp: 191-210, Academic Press
92. Panickar KS, Jewell DE. (2017). Anti-inflammatory Dietary Ingredients, Medicinal Plants, and Herbs Exert Beneficial Health Effects in Aging, Editor(s): Ronald Ross Watson, Nutrition and Functional Foods for Healthy Aging, Chapter 21, pp: 245-255, Academic Press
93. Chiara F, Salvatore FP, Colantuono F, Fiore M. Functional foods for elderly people: new paths for multi "functional" agriculture. *Open Agricult*. 2019; 4(1): 530-543.
94. Atlante A, Amadoro G, Bobba A, et al. Functional foods: An approach to modulate molecular mechanisms of Alzheimer's disease. *Cells*. 2020; 9(11):2347.
95. Uddin MS, Kabir MT, Al Mamun A, et al. Exploring potential of alkaloidal phytochemicals targeting neuroinflammatory signaling of Alzheimer's disease. *Curr Pharm Des*. 2020; 27(3):357-366.

96. Hasnieza Mohd Rosli N, Mastura Yahya H, Shahar S, et al. Alzheimer's disease and functional foods: An insight on neuroprotective effect of its combination. *Pak J Biol Sci.* 2020; 23(5):575-589.
97. Teibo J, Samuel B, Olagunju A, et al. Functional foods and bioactive compounds: Roles in the prevention, treatment and management of neurodegenerative diseases. *GSC Biol Pharmaceut Sci.* 2020; 11(02), 297–313.
98. Donma MM, Donma O, Michalke B, Halbach S, Nischwitz V. (2012). Vitamins, Minerals and Metabolic Pathways in Health and Diseases with a Special Chapter on Speciation. Vitamins, Macrominerals, Electrolytes, Trace Elements and Toxic Metals. Istanbul, Turkey, Istanbul University Publishing House
99. Ahmad R, Srivastava S, Ghosh S, et al. Phytochemical delivery through nanocarriers: A review. *Colloids Surf B Biointerfaces.* 2021; 197:111389.

Chapter 11

CURRENT NUTRITIONAL APPROACHES IN MANAGING PARKINSON'S DISEASE

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INTRODUCTION

Paralysis Agitans (Parkinson's Disease), a special motor dysfunction, was first defined by James Parkinson in 1817. In 1919, it was reported that the most important anomaly of Parkinson's disease (PD) is the loss of the neurons in the midbrain (1, 2). In the 1950s, researchers discovered that dopamine, which leads to understanding the pathophysiology and pathological biochemistry of PD, is depleted in the basal ganglia. Approximately 80% reduction in dopamine concentration drives to tremor, rigidity, akinesia/bradykinesia and postural instability, which are the main symptoms of the disease (3). These symptoms are defined as Parkinsonism and are considered to be a result of the progressive degeneration of dopaminergic neurons (4, 5).

Parkinson's disease is a slowly progressing chronic disease which usually starts between the ages 50 and 60 (6). Although various studies have been carried out to develop science-based therapies, the etiology of Parkinson's disease has not been fully clarified. It is reported that it is a non-inherited disease associated with environmental factors (water, herbicides, pesticides, chemicals) (7). If the disease starts at the age of 20, it is called primary juvenile parkinsonism, and if it starts between the ages 20 and 40, it is called young onset parkinsonism (6). This disease is observed in 1-2% of individuals aged 55 and above (8). At least two signs of Parkinsonism are seen in 15% of individuals between the ages 65-74, 30% of individuals between the ages 75-84, and more than 50% of the individuals over 85. The disease is 1.5 times more common in men than in women (6), and 4 times higher in the white race than in the black race (9). When the natural course of the disease is examined, it is seen that although the disease is significantly benign in some cases, 66% of the patients have symptoms of motor dysfunction in 5 years, while 80% of the patients have these symptoms in 10 years(10).

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REFERENCES

1. Goetz CG. Charcot and Parkinson's disease. In Parkinson's disease diagnosis and clinical management. S. Factor and W. Weiner, editors. Demos Medical Publishing. New York, New York, USA. 2002.19–26.
2. Hornykiewicz O. The discovery of dopamine deficiency in the parkinsonian brain. *J Neural Transm Suppl.* 2006;(70):9-15.
3. Baroni L, Zuliani C. A Plant-Food Diet in the Risk and Management of Parkinson's Disease. *Bioactive Nutraceuticals and Dietary Supplements in Neurological and Brain Disease.* Chapter 43, Elsevier, 2015
4. Raza C, & Anjum, R. Parkinson's disease: Mechanisms, translational models and management strategies. *Life sciences,* 2019;226, 77-90.
5. Gallo, V., Chen, H., & Pearce, N. (2020). Idiopathic Parkinson's disease and classification of parkinsonisms. *Oxford Textbook of Neurologic and Neuropsychiatric Epidemiology,* 93.
6. Van Bulck, M., Sierra-Magro, A., Alarcon-Gil, J., Perez-Castillo, A., & Morales-Garcia, J. A. Novel approaches for the treatment of Alzheimer's and Parkinson's disease. *International journal of molecular sciences,* (2019). 20(3), 719.
7. Lister, T. (2020). Nutrition and Lifestyle Interventions for Managing Parkinson's Disease: A Narrative Review. *Journal of Movement Disorders,* 13(2), 97-104.
8. Jankovic, J., & Tan, E. K. (2020). Parkinson's disease: etiopathogenesis and treatment. *Journal of Neurology, Neurosurgery & Psychiatry,* 91(8), 795-808.
9. Akbulut G. Parkinson Hastalığı ve Tibbi Beslenme Tedavisi. *Dirim Tıp Gazetesi* 2009; 84 (2):51-58.
10. Victor M, Ropper AH: Adams and Victor's principles of neurology, ed 8, New York, 2005, McGraw-Hill, Health Professions Division.
11. Agarwal P, Wang Y, Buchman AS, Holland TM, Bennett DA, Morris MC. MIND diet associated with reduced incidence and delayed progression of parkinsonism in old age. *J Nutr Health Aging* 2018;22:1211-1215
12. Taghizadeh M, Tamtaji OR, Dadgostar E, Daneshvar Kakhaki R, Bahmani F, Abolhassani J, et al. The effects of omega-3 fatty acids and vitamin E co-supplementation on clinical and metabolic status in patients with Parkinson's disease: a randomized, double-blind, placebo-controlled trial. *Neurochem Int* 2017;108:183-189.
13. Seidl SE, Santiago JA, Bilyk H, Potashkin JA, The emerging role of nutrition in Parkinson's disease. *Front Aging Neurosci.* 2014; 6:36
14. Baroni L, Zuliani C. Ensuring good nutritional status in patients with Parkinson's disease: challenges and solutions. *Research and Reviews in Parkinsonism* 2014. 4: p. 77-90.
15. Kurtis, M. M., & Pareés, I. (2020). Functional movement disorder comorbidity in Parkinson's disease: Unraveling the web. *Parkinsonism & Related Disorders.* <https://doi.org/10.1016/j.parkreldis.2020.10.022>
16. Schlickewei, O., Nienstedt, J. C., Frank, U., Fründt, O., Pötter-Nerger, M., Gerloff, C., ... & Pflug, C. (2020). The ability of the eating assessment tool-10 to detect penetration and aspiration in Parkinson's disease. *European Archives of Oto-Rhino-Laryngology,* 1-8.
17. Davies KN, King D, Davies H. A study of the nutritional status of elderly patients with Parkinson's disease. *Age and Ageing* 1994; 23: 142-145.
18. Barichella M, Akpalu A, Cham M, Privitera G, Cassani E, Cereda E, et al. Nutritional status and dietary habits in Parkinson's disease patients in Ghana. 2013;29(2): 470-473.
19. Leclercq C, Arcella D, Piccinelli R, Sette S, Le Donne C, Turrini A. The Italian National Food Consumption Survey INRAN-SCAI 2005-06: main results in terms of food consumption. *Public Health Nutr* 2009;12: 2504–32.
20. van der Marck MA, Dicke HC, Uc EY, Kentin ZH, Borm GF, Bloem BR, et al. Body mass index in Parkinson's disease: a meta-analysis. *Parkinsonism Relat Disord.* 2012;18(3):263-7
21. Sheard JM, Ash S, Silburn PA, Kerr GK, Prevalence of malnutrition in Parkinson's disease: a systematic review. *Nutr Rev.* 2011;69(9):520-32.

22. Baysal A, Sinir sistemi hastalıklarında beslenme. “Diyet El Kitabı” İn: Baysal A, Bozkurt N, Pekcan C, Besler HT, Aksoy M, Kutluay Merdol T, Keçecioglu S, Mercanlıgil S, eds. 3. Baskı. Ankara: Hatiboğlu Yayınevi, 2008.
23. Hayes MT, Parkinson’s Disease and Parkinsonism. *Am J Med.* 2019 Jul;132(7):802-807
24. Li, W. W. (2020). Botanical Therapeutics for Parkinson’s Disease. *Chinese Journal of Integrative Medicine*, 26, 405-411.
25. Çakmur R, Dönmez Çolakoğlu B, et al. Parkinson hastalığının tedavisinde kanıta dayalı yaklaşım. *Türkiye Klinikleri Nöroloji* 2008; 4: 51-59.
26. Stowe RL, Ives NJ, Clarke C, van Hilten J, Ferreira J, Hawker RJ, et al. Dopamine agonist therapy in early Parkinson’s disease. *Cochrane Database Syst Rev.* 2008 16;(2):CD006564.
27. Patil SA, Apine OA, Surwase SN, Jadhav JP. Biological sources of L-DOPA: An alternative approach. *Advances in Parkinson’s Disease* 2013;2(3):81-87.
28. Apaydin, H., S. Ertan, and S.J.M.d.o.j.o.t.M.D.S. Özekmekçi, Broad bean (*Vicia faba*)—A natural source of L-dopa—Prolongs “on” periods in patients with Parkinson’s disease who have “on-off” fluctuations. 2000;15(1):164-166.
29. Verni M, Coda R, Rizzello CG, The Use of Faba Bean Flour to Improve the Nutritional and Functional Features of Cereal-Based Foods: Perspectives and Future Strategies, in *Flour and Breads and their Fortification in Health and Disease Prevention.* 2019, Elsevier. p. 465-475.
30. Mohseni Mehran SM, Golshani B. Simultaneous Determination of Levodopa and Carbidopa from Fava Bean, Green Peas and Green Beans by High Performance Liquid Gas Chromatography. *Journal of Clinical and Diagnostic Research.* 2013;7(6):1004-100.
31. Kanazawa K, Sakakibara H. High Content of Dopamine, a Strong Antioxidant, in Cavendish Banana. *J Agric Food Chem.* 2000;48(3):844-8
32. Kema IP1, Schellings AM, Meiborg G, Hoppenbrouwers CJ, Muskiet FA. Influence of a Serotonin- and Dopamine-Rich Diet on Platelet Serotonin Content and Urinary Excretion of Biogenic Amines and Their Metabolites. *Clin Chem.* 1992;38(9):1730-6.
33. Green K. Best practice guideline for dietitians on the management of Parkinson’s. Birmingham, UK: British Dietetic Association. (2010).
34. Mahan LK, Escott-Stump S. *Krause’s Food, Nutrition and Diet Therapy*, 13th Edition, Elsevier, Pennsylvania, 2012, Chapter 41, 952-955.
35. Mena I, Cotzias GC, Protein intake and treatment of Parkinson’s disease with levodopa. *N Engl J Med* 1975;292, 181–184.
36. Marczewska A, De Notaris R, Sieri S, Barichella M, Fusconi E, Pezzoli G, Protein intake in parkinsonian patients using the EPIC food frequency questionnaire. *Mov. Disord.* 2006;21:1229–1231.
37. Khor SP, Hsu A, The pharmacokinetics and pharmacodynamics of Levodopa in the treatment of Parkinson’s disease. *Curr Clin Pharmacol.* 2007;2, 234–243.
38. Barichella M, Marczewska A, De Notaris R, Vairo A, Baldo C, Mauri A, Special low-protein foods ameliorate postprandial off in patients with advanced Parkinson’s disease. 2006;21(10): p. 1682-1687.
39. Carter JH, Nutt JG, Woodward WR, Hatcher LE, Trotman TL. Amount and distribution of dietary protein affects clinical response to levoDOPA in Parkinson’s disease. *Neurology* 1989;39:552–6.
40. Pare S, Barr SI, Ross SE, Effect of daytime protein restriction on nutrient intakes of free-living Parkinson’s disease patients. *Am J Clin Nutr.* 1992;55:701–707.
41. Karstaedt PJ, Pincus JM. Protein redistribution diet remains effective in patients with fluctuating parkinsonism. *Arch Neurol* 1992;49:149–51.
42. Mortaş H, Karaçil Ermumcu MŞ, Ayhan B, Akbulut G. *Tıbbi Beslenme Tedavisinde Güncel Uygulamalar IV. Nörolojik Hastalıklarda Tıbbi Beslenme Tedavisi Türkiye.* Ankara Nobel Tıp Kitabevleri. (2015).
43. Shahpiri Z, Bahramsoltani R, Hosein Farzaei M, Farzaei F, Rahimi R., Phytochemicals as future drugs for Parkinson’s disease: a comprehensive review. 2016;27(6): 651-668.

44. Gao X, Chen H, Fung TT, Logroscino G, Schwarzschild MA, Hu FB, et al. Prospective study of dietary pattern and risk of Parkinson disease. *Am J Clin Nutr* 2007;86, 1486–1494.
45. Okubo H, Miyake Y, Sasaki S, Murakami K, Tanaka K, Fukushima W et al. Dietary patterns and risk of Parkinson's disease: a case-control study in Japan. *Eur J Neurol* 2012;19, 681–688
46. Logroscino G, Sesso HD, Paffenbarger RS Jr, Lee IM. Body mass index and risk of Parkinson's disease: a prospective cohort study. *Am J Epidemiol* 2007;166:1186–1190.
47. Da Silva TM, Munhoz RP, Alvarez C, Naliwaiko K, Kiss A, Andreatini R, et al.. Depression in Parkinson's disease: a double-blind, randomized, placebo-controlled pilot study of omega-3 fatty-acid supplementation. *J Affect Disord* 2008;111, 351–359.
48. Bajracharya, R., Youngson, N. A., & Ballard, J. W. O. (2019). Dietary macronutrient management to treat mitochondrial dysfunction in Parkinson's disease. *International journal of molecular sciences*, 20(8), 1850.
49. Murakami K, Miyake Y, Sasaki S, Tanaka K, Fukushima W, Kiyohara C, et al. Dietary intake of folate, vitamin B6, vitamin B12 and riboflavin and risk of Parkinson's disease: a case-control study in Japan. *Br J Nutr*. 2010;104(5):757-64
50. Marashly ET, Bohlega SA, Riboflavin has neuroprotective potential: focus on Parkinson's disease and migraine. *Front Neurol*. 2017;8:333
51. Shen L, Associations between B vitamins and Parkinson's disease. *Nutrients*. 2015; 7(9):7197-208
52. Gleichmann M, Mattson MP. Neuronal calcium homeostasis and dysregulation. *Antioxidants & redox signaling*, 2011;14(7), 1261-1273.
53. Larsson SC, Singleton AB, Nalls MA, Richards JB; International Parkinson's Disease Genomics Consortium (IPDGC). No clear support for a role for vitamin D in Parkinson's disease: A Mendelian randomization study. *Mov Disord*. 2017;32(8):1249-1252.
54. Zhou Z, Zhou R, Zhang Z, Li K, The Association Between Vitamin D Status, Vitamin D Supplementation, Sunlight Exposure, and Parkinson's Disease: A Systematic Review and Meta-Analysis. *Med Sci Monit*. 2019;23(25):666-674
55. Kim HD, Jeong KH, Jung UJ, Kim SR, Naringin treatment induces neuroprotective effects in a mouse model of Parkinson's disease in vivo, but not enough to restore the lesioned dopaminergic system. *J Nutr Biochem*. 2016;28:140-6
56. Leem E, Nam JH, Jeon MT, Shin WH, Won SY, Park SJ, et al. Naringin protects the nigrostriatal dopaminergic projection through induction of GDNF in a neurotoxin model of Parkinson's disease. *J Nutr Biochem*. 2014;25(7):801-6
57. Jung UJ, Leem E, Kim SR. Naringin: a protector of the nigrostriatal dopaminergic projection. *Exp Neurobiol*. 2014;23(2):124-9.
58. Alcalay RN, Gu Y, Mejia-Santana H, Cote L, Marder KS, Scarmeas N (2012). The association between Mediterranean diet adherence and Parkinson's disease. *Mov Disord*. 2012;27(6):771-4
59. Maraki MI, Yannakoulia M, Stamelou M, Stefanis L, Xiromerisiou G, Kosmidis MH, et al. Mediterranean diet adherence is related to reduced probability of prodromal Parkinson's disease. *Mov Disord* 2019;34(1): p. 48-57.
60. Paknahad, Z., Sheklabadi, E., Moravejolahkami, A. R., Chitsaz, A., & Hassanzadeh, A. (2020). The effects of Mediterranean diet on severity of disease and serum Total Antioxidant Capacity (TAC) in patients with Parkinson's disease: a single center, randomized controlled trial. *Nutritional Neuroscience*, 1-8.
61. Munoz DG, Fujioka S, Caffeine and Parkinson disease: A possible diagnostic and pathogenic breakthrough. *Neurology*. 2018; 30;90(5):205-206
62. Deleu D, Jacob P, Chand P, Sarre S, Colwell A. Effects of caffeine on levodopa pharmacokinetics and pharmacodynamics in Parkinson disease. *Neurology*, 2006; 67(5), 897-899.
63. Hu G, Bidel S, Jousilahti P, Antikainen R, Tuomilehto J. Coffee and tea consumption and the risk of Parkinson's disease. *Mov Disord* 2007;22,2242–2248. doi:10.1002/mds.21706.
64. Chen W, Wang H, Wei H, Gu S, Wei H. Istradefylline, an adenosine A2A receptor antagonist, for patients with Parkinson's disease: a meta-analysis. *Journal of the Neurological Sciences*

- 2013; 324(1-2): 21-28
65. Morris JK, Bomhoff GL, Stanford JA, Geiger PC. Neuro degeneration in an animal model of Parkinson's disease exacerbated by a high-fat diet. *Am J Physiol Regul Integr Comp Physiol*. 2010 Oct; 299(4): R1082-R1090
 66. Bousquet M, St-Amour I, Vandal M, Julien P, Cicchetti F, Calon F. High-fat diet exacerbates MPTP-induced dopaminergic degeneration in mice. *Neurobiol Dis* 2011; 45, 529-538. doi:10.1016/j.nbd.2011.09.009
 67. Sharma S, Taliyan R. High fat diet feeding induced insulin resistance exacerbates 6-OHDA mediated neurotoxicity and behavioral abnormalities in rats. *Behav Brain Res*, 2018; **351**: p. 17-23.
 68. Dong J, Beard JD, Umbach DM, Park Y, Huang X, Blair A, et al. Dietary fat intake and risk for Parkinson's disease. 2014; **29**(13): p. 1623-1630.
 69. Qu Y, Chen X, Xu MM, Sun Q. Relationship between high dietary fat intake and Parkinson's disease risk: a meta-analysis. 2019; **14**(12): p. 2156.
 70. Chen H, O'Reilly E, McCullough ML, Rodriguez C, Schwarzschild MA, Calle EE, et al. Consumption of dairy products and risk of Parkinson's disease. 2007; **165**(9): p. 998-1006.
 71. Sääksjärvi K, Knekt P, Lundqvist A, Männistö S, Heliövaara M, Rissanen H, et al. A cohort study on diet and the risk of Parkinson's disease: the role of food groups and diet quality. 2013; **109**(2): p. 329-337.
 72. Gao X, O'Reilly EJ, Schwarzschild MA, Ascherio A. Prospective study of plasma urate and risk of Parkinson disease in men and women. 2016. **86**(6): p. 520-526.
 73. Weisskopf MG, O'Reilly E, Chen H, Schwarzschild MA, Ascherio A. Plasma urate and risk of Parkinson's disease. 2007; **166**(5): p. 561-567.
 74. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. 2004; **350**(11): p. 1093-1103.
 75. Hughes KC, Gao X, Kim IY, Wang M, Weisskopf MG, Schwarzschild MA et al. Intake of dairy foods and risk of Parkinson disease. 2017; **89**(1): p. 46-52.
 76. Kyrozis A, Ghika A, Stathopoulos P, Vassilopoulos D, Trichopoulos D, Trichopoulou A.. Dietary and lifestyle variables in relation to incidence of Parkinson's disease in Greece. *European journal of epidemiology*, 2013; **28**(1), 67-77.
 77. Kalia LV, Lang AE. Parkinson's disease. *Lancet*, 2015. **386**(9996): p. 896-912.
 78. Chen H, Zhang SM, Hernán MA, Willett WC, Ascherio A. Diet and Parkinson's disease: a potential role of dairy products in men. *Annals of neurology*, 2002;**52**(6), 793-801.
 79. Corrigan FM, Wienburg CL, Shore RF, Daniel SE, Mann D. Organochlorine insecticides in substantia nigra in Parkinson's disease. *Journal of toxicology and environmental health Part A*, 2000;**59**(4), 229-234.
 80. Sato Y, Yasumiishi C, Chiba T, Umegaki K. A systematic review to identify unacceptable intake levels of vitamin B6 among patients taking levodopa. 2017;**58**(6):268-274
 81. Leon AS, Spiegel HE, Thomas G, Abrams WB. Pyridoxine antagonism of levodopa in parkinsonism. *JAMA*. 1971;**218**:1924-1927.
 82. Harold Mars, MD, .Levodopa, Carbidopa, and Pyridoxine in Parkinson Disease. *Arch Neurol*. 1974;**30**(6):444-447.
 83. Bender DA, C. Earl CJ, Lees AJ, Niacin depletion in Parkinsonian patients treated with L-dopa, benserazide and carbidopa. 1979;**56**(1): p. 89-93.
 84. Garfinkel HA. Banana and L-dopa. *British Medical Journal*, 1972;**1**(5795), 312.
 85. Ogo Y, Sunagane N, Ohta T, Uruno T. Banana juice reduces bioavailability of levodopa preparation. *Yakugaku Zasshi* 2005, **125**, 1009-1011.

Chapter 12

PANDEMIC ORGANIZATION IN THE EMERGENCY SERVICE

Ensar DURMUŞ¹

INTRODUCTION

The disease caused by the virus called SARS-CoV-22, which emerged at the end of 2019 in Wuhan, Hubei Province, China, was named COVID-19. The disease spread within a few weeks and caused a declaration of worldwide pandemic by the World Health Organization (1). Many countries had to take measures such as closing their country borders to the passage of other country citizens, stopping international flights, imposing curfews, and imposing a mask on people to protect themselves from the effect of this spreading virus (2). Despite all the precautions, the virus continued to spread to Europe and America. In particular, countries such as Spain, Italy, the United States of America and Brazil were among the leading countries that were badly affected by the pandemic.

SARS-CoV-2 virus is an enveloped mRNA virus from the Coronavirus family. It may infect bronchial epithelial cells, pneumocyte cells and upper respiratory tract, causing life-threatening respiratory diseases and clinical pictures that progress to lung damage (3). In this disease, for which there is no known specific treatment, patients may be asymptomatic or present with severe respiratory failure. It has become an important cause of mortality and morbidity today due to its adverse effects on the respiratory and cardiovascular system (4).

As of the first days of 2021, 90,335,008 confirmed COVID-19 cases and 1,954,336 deaths due to COVID-19 have been reached in 223 countries (5). Due to this pessimistic picture, the economies of the countries were also badly affected by the pandemic, and 25,000,000 people faced the danger of unemployment worldwide due to Covid-19 (6). Of course, as a result of this situation, there has been an increase in diseases such as depression and an increase in the number of suicides that also impair public health psychologically (7). Thus, Covid-19 disease has become at the top of the world health agenda by affecting the health of societies with both its physiological effects and psychological traumas.

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CONCLUSION

Emergency services are one of the most used units during pandemic periods. It will be beneficial to make measures and arrangements such as making an effective and good triage in these areas, dividing the emergency services into areas according to the patient groups, arranging the working hours and schedules of the employees, having a sufficient number of health workers, establishing a strong communication network among emergency workers. During the pandemic period, which is a dynamic process, measures appropriate to the needs should be taken on time.

REFERENCES

1. WHO announces COVID-19 outbreak a pandemic (Internet). World Health Organization; 2020 (cited 2020 Apr 11). Available from: <http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic>
2. Nicola M, Alsafi Z, Sohrabi C, Kerwan A, Al-Jabir A, Iosifidis C, et al. The socio-economic implications of the coronavirus pandemic (COVID-19): A review. *Int J Surg*. 2020 Jun;78:185–93.
3. V'kovski P, Kratzel A, Steiner S, Stalder H, Thiel V. Coronavirus biology and replication: implications for SARS-CoV-2. *Nature Reviews Microbiology*. 2020 Oct 28;1–16.
4. Sparks Matthew A., South Andrew M., Badley Andrew D., Baker-Smith Carissa M., Battle Daniel, Bozkurt Biykem, et al. Severe Acute Respiratory Syndrome Coronavirus 2, COVID-19, and the Renin-Angiotensin System. *Hypertension*. 2020 Nov 1;76(5):1350–67.
5. CDC. Coronavirus Disease 2019 (COVID-19) - Transmission (Internet). Centers for Disease Control and Prevention. 2020 (cited 2021 Jan 15). Available from: <https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/how-covid-spreads.html>
6. Almost 25 million jobs could be lost worldwide as a result of COVID-19, says ILO (Internet). 2020 (cited 2021 Jan 15). Available from: https://www.ilo.org/global/about-the-ilo/newsroom/news/WCMS_738742/lang--en/index.htm
7. Kawohl W, Nordt C. COVID-19, unemployment, and suicide. *The Lancet Psychiatry*. 2020 May;7(5):389–90.
8. Shoja E, Aghamohammadi V, Bazayr H, Moghaddam HR, Nasiri K, Dashti M, et al. Covid-19 effects on the workload of Iranian healthcare workers. *BMC Public Health*. 2020 Nov 2;20(1):1636.
9. Lucchini A, Elli S, De Felippis C, Greco C, Mulas A, Ricucci P, et al. The evaluation of nursing workload within an Italian ECMO Centre: A retrospective observational study. *Intensive and Critical Care Nursing*. 2019 Dec 1;55:102749.
10. Lucchini A, Iozzo P, Bambi S. Nursing workload in the COVID-19 era. *Intensive Crit Care Nurs*. 2020 Dec;61:102929.
11. Vizheh M, Qorbani M, Arzaghi SM, Muhidin S, Javanmard Z, Esmaeili M. The mental health of healthcare workers in the COVID-19 pandemic: A systematic review. *J Diabetes Metab Disord*. 2020 Oct 26;1–12.
12. Shaukat N, Ali DM, Razzak J. Physical and mental health impacts of COVID-19 on healthcare workers: a scoping review. *Int J Emerg Med*. 2020 Dec;13(1):40.
13. Heymann EP, Exadaktylos A. How the COVID-19 pandemic illustrated the importance of emergency medicine, and its vital role as a pillar of the healthcare system. *Emerg Med J*. 2020 Jul;37(7):411–411.
14. Schreyer KE, del Portal DA, King LJJ, Blome A, DeAngelis M, Stauffer K, et al. Emergency Department Management of the Covid-19 Pandemic. *The Journal of Emergency Medicine*. 2020 Dec 1;59(6):946–51.

15. Jeffery MM, D'Onofrio G, Paek H, Platts-Mills TF, Soares WE, Hoppe JA, et al. Trends in Emergency Department Visits and Hospital Admissions in Health Care Systems in 5 States in the First Months of the COVID-19 Pandemic in the US. *JAMA Intern Med.* 2020 Oct 1;180(10):1328.
16. Quah LJJ, Tan BKK, Fua T-P, Wee CPJ, Lim CS, Nadarajan G, et al. Reorganising the emergency department to manage the COVID-19 outbreak. *International Journal of Emergency Medicine.* 2020 Jun 17;13(1):32.
17. Hartnett KP. Impact of the COVID-19 Pandemic on Emergency Department Visits — United States, January 1, 2019–May 30, 2020. *MMWR Morb Mortal Wkly Rep (Internet).* 2020 (cited 2021 Jan 15);69. Available from: <https://www.cdc.gov/mmwr/volumes/69/wr/mm6923e1.htm>
18. Alper M. Top 100 Hospitals in Each Branch-2017 Number of Public Hospitals Examination, Hospitalization, Intensive Care, Surgery, Emergency Service and Births (Internet). Türkiye Cumhuriyeti Sağlık Bakanlığı Kamu Hastaneleri Genel Müdürlüğü İstatistik, Analiz, Raporlama ve Stratejik Yönetim Dairesi Başkanlığı; 2017 (cited 2020 Mar 12). Available from: <https://khgmistatistikdb.saglik.gov.tr/TR,43819/her-bransta-ilk-100-hastane-2017-yili-kamu-hastaneleri-muayene-yatis-yogun-bakim-ameliyat-acil-servis-ve-dogum-sayilari.html>
19. Ersel M, Karcioğlu O, Yanturalı S, Yuruktumen Ünal A, Sever M, Tunc MA. Emergency department utilization characteristics and evaluation for patient visit appropriateness from the patients' and physicians' point of view. (Article in Turkish) *Turk J Emerg Med.* 2006 Apr 1;6:25–35.
20. Altıntop I, Tatlı M. Acil servis yoğunluğuna farklı bir bakış: anket çalışması. *Journal of Anatolian Medical Research.* 2017 May 22;2(1):45–57.
21. Yataklı Sağlık Tesislerinde Acil Servis Hizmetlerinin Uygulama Usul ve Esasları Hakkında Tebliğde Değişiklik Yapılmasına Dair Tebliğ (İnternet). Feb 20, 2018. Available from: <https://www.resmigazete.gov.tr/eskiler/2018/02/20180220-4.htm>
22. Mitchell R, Banks C. Emergency departments and the COVID-19 pandemic: making the most of limited resources. *Emerg Med J.* 2020 May 1;37(5):258–9.
23. Durmuş E, Güneysu F. Effect of COVID-19 on the admissions to the adult emergency department. *J Contemp Clin Pract.* 2020 Nov;6(2):58–63.
24. Giamello JD, Abram S, Bernardi S, Lauria G. The emergency department in the COVID-19 era. Who are we missing? *European Journal of Emergency Medicine.* 2020 Aug;27(4):305–6.
25. Kunt MM, Karaca MA. COVID 19 Pandemisi ve Acil Servis Triyajı. *Anatolian Journal of Emergency Medicine.* 2020 Sep 30;3(3):96–8.
26. Park J-H, Lee S-G, Ahn S, Kim JY, Song J, Moon S, et al. Strategies to prevent COVID-19 transmission in the emergency department of a regional base hospital in Korea: From index patient until pandemic declaration. *Am J Emerg Med (Internet).* 2020 Jul 24 (cited 2021 Jan 18); Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7378011/>
27. Masoni M, Guelfi MR. WhatsApp and other messaging apps in medicine: opportunities and risks. *Intern Emerg Med.* 2020 Mar 1;15(2):171–3.
28. RCN Members will explore nursing shifts patterns and patient safety (Internet). The Royal College of Nursing. (cited 2021 Jan 18). Available from: </news-and-events/news/unpredictable-shifts-101120>
29. Iswanto A. Innovative Work Shift for Health Workers in the Health Service Providers in Handling COVID-19 Cases. *Kesmas: National Public Health Journal.* 2020 Jul 27;15.
30. Kluger DM, Aizenbud Y, Jaffe A, Parisi F, Aizenbud L, Minsky-Fenick E, et al. Impact of healthcare worker shift scheduling on workforce preservation during the COVID-19 pandemic. *Infect Control Hosp Epidemiol.* :1–3.
31. Van Zundert TCRV, Van Overloop J, Tran DQ, Van Zundert AAJ. Operating 12-Hour Staff Shifts on Coronavirus Disease-2019 Patients: A Harmful and Unwanted Proposal. *Anesth Analg (Internet).* 2020 Sep 1 (cited 2021 Jan 18); Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7469596/>