

Bölüm 1

POLİKİSTİK OVER SENDROMUNUN COVID-19 HASTALIĞI SEYRİNDEKİ YERİ

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Giriş

Polikistik over sendromu, 1935 yılında Stein ve Leventhal tarafından¹ “polikistik overler ve amenore birlikteliği” şeklinde ifade edilmiştir. Kelime anlamına bakıldığında “poli” çok sayıda; “kistik” kist içeren anlamındadır ve “polikistik over” çok sayıda kist içeren yumurtalık dokusuna işaret etmektedir. Polikistik over sendromu (PKOS) ise doğurgan dönemdeki kadınları etkileyen, kronik anovülasyon ve hiperandrojenizm ile karakterize, multifaktöriyel bir hastalıktır.² İncelenen popülasyona ve uygulanan tanı kriterlerine bağlı olarak PKOS, üreme çağındaki kadınlarda $\geq$ %10-15 oran ile en sık görülen endokrin bozukluktur.^{3,4} Ancak sık görülmesine rağmen, altta yatan etiyolojisi ve patofizyolojisi halen tam olarak açıklığa kavuşmamıştır. PKOS, klinikte menstrüel düzensizlik, hirsutizm, akne, alopesi ve özellikle 1. trimesterde tekrarlayan gebelik kayıpları ile ilişkilendirilmektedir. Endokrinoloji yönünden yükselmiş androjen, luteinizan hormon (LH), östrojen ve prolaktin düzeyleri öne çıkarken; metabolik olarak insülin direnci (İD), Tip 2 Diabetes Mellitus (T2DM), dislipidemi, obezite, kalp-damar hastalıkları, psikiyatrik/nörolojik bozukluklar ve jinekolojik kanserlerle de ilişkilendirilmektedir.^{5,6}

Günümüzde PKOS tanısında, Rotterdam’ da 2003 yılında düzenlenmiş olan ESHRE/ASRM konferansında belirlenen ya da 2006 yılında AE-PCOS (Androjen Fazlalığı ve Polistik Over Sendromu Topluluğu) konferansında kararlaştırılan kriterler kullanılmaktadır.³ İlgili bozuklukların (hiperprolaktinemi, hipotiroidizm ve klasik olmayan konjenital adrenal hiperplazi vb.) dışlanması ardından, hem over disfonksiyonu (kronik oligo - veya anovülasyon) hem de hiperandrojenizm (hirsutizm ve/veya artmış serbest testosteron ya da serbest androjen indeksi) varlığı PKOS tanısı için gereklidir. Ultrasonda polikistik over morfolojisi de Rotterdam tanı kriterleri^{3,4,7} arasında yer almaktadır.

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gibi metabolik patolojilerle de yakın ilişkilidir. Kronik inflamatuvar bir süreç olan şeker hastalığının özellikle T2DM'li kişilerde patojenlere cevabı olumsuz etkilediği, pnömoni enfeksiyonunun daha ağır geçirilmesine neden olduğu gösterilmiştir. Bu bağlamda değerlendirildiğinde, solunum sistemini tehdit eden SARS-CoV-2 enfeksiyonunun PKOS' lu kadınlarda ağır seyretme olasılığı yüksektir.

KAYNAKLAR

1. Stein, IF, Leventhal, NL. Amenorrhea associated with bilateral polycystic ovaries. American Journal Of Obstetrics And Gynecology, . 1935; 29, 181.
2. Witchel, S.F. (2007). Hirsutism and polycystic ovary syndrome. In: Lifshitz F (Ed.), Pediatric Endocrinology (pp 325-48). New York, Informa Healthcare USA Inc.
3. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Human Reproduction, 2004; 19 (1), 41-7. doi: 10.1093/humrep/deh098.
4. Kyrou, I., Weickert, M.O., Randevara, H.S.(2015). Diagnosis and management of polycystic ovary syndrome (PCOS). In: Ajjan, R., Orme, S.M.(Eds.), Endocrinology and Diabetes (p.99-113). London: Springer.
5. Goodarzi MO, Dumesic DA, Chazenbalk G, et al. Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. Nature Reviews Endocrinology, 2011; 7(4),219-31. doi: 10.1038/nrendo.2010.217.
6. Vrbikova J, Hainer V. Obesity and polycystic ovary syndrome. Obesity Facts, 2009; 2 (1), 26-35. doi: 10.1159/000194971.
7. Teede HJ, Misso ML, Costello MF, et al. International PCOS Network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertility and Sterility, 2018; 110 (3), 364-379. doi: 10.1016/j.fertnstert.2018.05.004.
8. WHO Director-General's opening remarks at the media briefing on COVID-19, 11 March 2020.
9. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 Pathophysiology: A review. Clinical Immunology, 2020; 215, 108427. doi: 10.1016/j.clim.2020.108427.
10. Jin JM, Bai P, He W, et al. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. Frontiers in Public Health, 2020; 29, 8152. doi: 10.3389/fpubh.2020.00152.
11. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020; 323 (20), 2052-2059. doi: 10.1001/jama.2020.6775. Erratum in: JAMA. 2020; 323 (20), 2098.
12. Bornstein SR, Dalan R, Hopkins D, et al. Endocrine and metabolic link to coronavirus infection. Nature Reviews Endocrinology, 2020; 16 (6), 297-298. doi: 10.1038/s41574-020-0353-9.
13. Aldridge RW, Lewer D, Katikireddi SV, et al. Black, Asian and Minority Ethnic groups in England are at increased risk of death from COVID-19: indirect standardisation of NHS mortality data. Wellcome Open Research, 2020; 5, 88. doi: 10.12688/wellcomeopenres.15922.2.
14. Pareek M, Bangash MN, Pareek N, et al. Ethnicity and COVID-19: an urgent public health research priority. Lancet, 2020; 395 (10234), 1421-1422. doi: 10.1016/S0140-6736(20)30922-3.

15. UK Office for National Statistics (2020). Coronavirus (COVID-19) related deaths by ethnic group, England and Wales: 2 March 2020 to 10 April 2020. <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/coronavirusrelated-deathsbyethnigroupenglandandwales/2march2020to10april2020>. Accessed 26.March.2021.
16. Liverpool L. Why are ethnic minorities worse affected? *New Scientist*, 2020; 246 (3279), 11. doi: 10.1016/S0262-4079(20)30790-9.
17. Zhang Y, Che L, Zhang M, et al. Common cytokine polymorphisms and predisposition to polycystic ovary syndrome: a meta-analysis. *Endocrine Journal*, 2020; 67 (5), 561-567. doi: 10.1507/endocrj.EJ19-0558.
18. Kakoly NS, Khomami MB, Joham AE, et al. Ethnicity, obesity and the prevalence of impaired glucose tolerance and type 2 diabetes in PCOS: a systematic review and meta-regression. *Human Reproduction Update*, 2018; 24 (4), 455-467. doi: 10.1093/humupd/dmy007.
19. Ding T, Hardiman PJ, Petersen I, et al. The prevalence of polycystic ovary syndrome in reproductive-aged women of different ethnicity: a systematic review and meta-analysis. *Oncotarget*, 2017; 8 (56), 96351-96358. doi: 10.18632/oncotarget.19180.
20. Wang S, Alvero R. Racial and ethnic differences in physiology and clinical symptoms of polycystic ovary syndrome. *Seminars in Reproductive Medicine*, 2013; 31 (5), 365-9. doi: 10.1055/s-0033-1348895.
21. Kyrrou I, Randeve HS, Tsigos C, et al (2018). Clinical Problems Caused by Obesity. In: Feingold KR, Anawalt B, Boyce A, et al.(Eds.), *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc. <https://www.ncbi.nlm.nih.gov/books/NBK278973/>. Accessed 20 March 2021.
22. Randeve HS, Tan BK, Weickert MO, et al. Cardiometabolic aspects of the polycystic ovary syndrome. *Endocrine Reviews*, 2012; 33 (5), 812-41. doi: 10.1210/er.2012-1003.
23. Kahal H, Kyrrou I, Tahrani AA, Randeve HS. Obstructive sleep apnoea and polycystic ovary syndrome: A comprehensive review of clinical interactions and underlying pathophysiology. *Clinical Endocrinology (Oxf)*. 2017; 87 (4), 313-319. doi: 10.1111/cen.13392.
24. Kyrrou I, Karteris E, Robbins T, et al. Polycystic ovary syndrome (PCOS) and COVID-19: an overlooked female patient population at potentially higher risk during the COVID-19 pandemic. *BMC Medicine*, 2020; 18(1),220. doi: 10.1186/s12916-020-01697-5.
25. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE 2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*, 2020; 181(2), 271-280.e8. doi: 10.1016/j.cell.2020.02.052.
26. Wambier CG, Vaño-Galván S, McCoy J, et al. Androgenetic alopecia present in the majority of patients hospitalized with COVID-19: The “Gabrin sign”. *Journal of The American Academy of Dermatology*, 2020; 83(2), 680-682. doi: 10.1016/j.jaad.2020.05.079.
27. Goren A, Vaño-Galván S, Wambier CG, et al. A preliminary observation: Male pattern hair loss among hospitalized COVID-19 patients in Spain- A potential clue to the role of androgens in COVID-19 severity. *Journal of Cosmetic Dermatology*, 2020; 19 (7), 1545-1547. doi: 10.1111/jocd.13443.
28. Glintborg D, Hass Rubin K, Nybo M, et al. Morbidity and medicine prescriptions in a nationwide Danish population of patients diagnosed with polycystic ovary syndrome. *European Journal of Endocrinology*, 2015; 172 (5), 627-38. doi: 10.1530/EJE-14-1108.
29. Htet TD, Teede HJ, de Courten B, et al. Asthma in reproductive-aged women with polycystic ovary syndrome and association with obesity. *European Respiratory Journal*, 2017; 49 (5), 1601334. doi: 10.1183/13993003.01334-2016.
30. Taneja V. Sex Hormones Determine Immune Response. *Frontiers in Immunology*, 2018; 9, 1931. doi: 10.3389/fimmu.2018.01931.

31. Fagone P, Ciurleo R, Lombardo SD, et al. Transcriptional landscape of SARS-CoV-2 infection dismantles pathogenic pathways activated by the virus, proposes unique sex-specific differences and predicts tailored therapeutic strategies. *Autoimmunity Reviews*, 2020; 19 (7), 102571. doi: 10.1016/j.autrev.2020.102571.
32. Klein SL, Flanagan KL. Sex differences in immune responses. *Nature Reviews Immunology*, 2016; 16 (10): 626-38. doi: 10.1038/nri.2016.90.
33. Barnes BJ, Adrover JM, Baxter-Stoltzfus A, et al. Targeting potential drivers of COVID-19: Neutrophil extracellular traps. *Journal of Experimental Medicine*, 2020; 217 (6), e20200652. doi: 10.1084/jem.20200652.
34. Schroeder M, Tuku B, Jarczak D, et al. The majority of male patients with COVID-19 present low testosterone levels on admission to Intensive Care in Hamburg, Germany: a retrospective cohort study. *medRxiv*, Preprint; 2020.
35. Ghosh S, Klein RS. Sex Drives Dimorphic Immune Responses to Viral Infections. *Journal of Immunology*, 2017; 198 (5), 1782-1790. doi: 10.4049/jimmunol.1601166.
36. Qiu Y, Zhao YB, Wang Q, et al. Predicting the angiotensin converting enzyme 2 (ACE2) utilizing capability as the receptor of SARS-CoV-2. *Microbes and Infection*, 2020; 22 (4-5), 221-225. doi: 10.1016/j.micinf.2020.03.003.
37. Dalpiaz PL, Lamas AZ, Caliman IF, et al. Sex Hormones Promote Opposite Effects on ACE and ACE2 Activity, Hypertrophy and Cardiac Contractility in Spontaneously Hypertensive Rats. *PLoS One*. 2015; 10 (5), e0127515. doi: 10.1371/journal.pone.0127515. Erratum in: *PLoS One*. 2015; 10 (7), e0133225.
38. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *International Journal of Oral Science*, 2020; 12 (1), 8. doi:10.1038/s41368-020-0074-x.
39. Jing Y, Run-Qian L, Hao-Ran W, et al. Potential influence of COVID-19/ACE2 on the female reproductive system. *Molecular Human Reproduction*, 2020; 26 (6), 367-373. doi: 10.1093/molehr/gaaa030.
40. McCoy J, Wambier CG, Vano-Galvan S, et al. Racial variations in COVID-19 deaths may be due to androgen receptor genetic variants associated with prostate cancer and androgenetic alopecia. Are anti-androgens a potential treatment for COVID-19? *Journal of Cosmetic Dermatology*, 2020; 19 (7), 1542-1543. doi: 10.1111/jocd.13455.
41. Wambier CG, Goren A. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is likely to be androgen mediated. *Journal of The American Academy of Dermatology*, 2020; 83 (1), 308-309. doi: 10.1016/j.jaad.2020.04.032.
42. La Vignera S, Cannarella R, Condorelli RA, et al. Sex-Specific SARS-CoV-2 Mortality: Among Hormone-Modulated ACE2 Expression, Risk of Venous Thromboembolism and Hypovitaminosis D. *International Journal Molecular Science*, 2020; 21 (8), 2948. doi: 10.3390/ijms21082948.
43. Wambier CG, Goren A, Vaño-Galván S, et al. Androgen sensitivity gateway to COVID-19 disease severity. *Drug Development Research*, 2020; 81 (7), 771-776. doi: 10.1002/ddr.21688.
44. Di Guardo F, Cerana MC, D'urso G, et al. Male PCOS equivalent and nutritional restriction: Are we stepping forward? *Medical Hypotheses*, 2019; 126, 1-3. doi: 10.1016/j.mehy.2019.03.003.
45. Cannarella R, Condorelli RA, Dall'Oglio F, et al. Increased DHEAS and Decreased Total Testosterone Serum Levels in a Subset of Men with Early-Onset Androgenetic Alopecia: Does a Male PCOS-Equivalent Exist? *International Journal of Endocrinology*, 2020; 2020, 1942126. doi: 10.1155/2020/1942126.
46. Schroeder M, Tuku B, Jarczak D, et al. The majority of male patients with COVID-19 present low testosterone levels on admission to Intensive Care in Hamburg, Germany: a retrospective cohort study. 2020. Preprint at <https://www.medrxiv.org/content/10.1101/2020.05.07.20073817v1>.

47. Pozzilli P, Lenzi A. Commentary: Testosterone, a key hormone in the context of COVID-19 pandemic. *Metabolism*. 2020;108, 154252. doi: 10.1016/j.metabol.2020.154252.
48. Harwood K, Vuguin P, DiMartino-Nardi J. Current approaches to the diagnosis and treatment of polycystic ovarian syndrome in youth. *Hormone Research*, 2007; 68 (5), 209-17. doi: 10.1159/000101538.
49. Kiddy DS, Sharp PS, White DM, et al. Differences in clinical and endocrine features between obese and non-obese subjects with polycystic ovary syndrome: an analysis of 263 consecutive cases. *Clinical Endocrinology (Oxf)*. 1990; 32 (2), 213-20. doi: 10.1111/j.1365-2265.1990.tb00857.x.
50. Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. *American Journal of Physiology- Endocrinology and Metabolism*, 2020; 318 (5), E736-E741. doi: 10.1152/ajpendo.00124.2020.
51. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020; 323 (13), 1239-1242. doi: 10.1001/jama.2020.2648.
52. www.icnarc.org. (Accessed March 11, 2021).
53. Simonnet A, Chetboun M, Poissy J, et al. High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. *Obesity (Silver Spring)*, 2020; 28 (7), 1195-1199. doi: 10.1002/oby.22831.
54. Tsatsanis C, Margioris AN, Kontoyiannis DP. Association between H1N1 infection severity and obesity-adiponectin as a potential etiologic factor. *Journal of Infectious Diseases*, 2010; 202 (3), 459-60. doi: 10.1086/653842. PMID: 20557238.
55. Barber TM, Hanson P, Weickert MO, et al. Obesity and Polycystic Ovary Syndrome: Implications for Pathogenesis and Novel Management Strategies. *Clinical Medicine Insights: Reproductive Health*, 2019; 13, 1179558119874042. doi: 10.1177/1179558119874042.
56. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*, 2020; 323 (11), 1061-1069. doi: 10.1001/jama.2020.1585. Erratum in: *JAMA*. 2021 Mar 16; 325 (11): 1113.
57. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*, 2020; 395 (10229), 1054-1062. doi: 10.1016/S0140-6736(20)30566-3. Epub 2020 Mar 11. Erratum in: *Lancet*, 2020; 395 (10229), 1038. Erratum in: *Lancet*. 2020 Mar 28; 395 (10229): 1038.
58. Azizpour Y, Delpisheh A, Montazeri Z, et al. Effect of childhood BMI on asthma: a systematic review and meta-analysis of case-control studies. *BMC Pediatrics*, 2018; 18 (1), 143. doi: 10.1186/s12887-018-1093-z.
59. Grewal G, Joshi GP. Obesity and Obstructive Sleep Apnea in the Ambulatory Patient. *Anesthesiology Clinics*, 2019; 37 (2), 215-224. doi: 10.1016/j.anclin.2019.01.001.
60. Fuller-Thomson E, Howden KEN, Fuller-Thomson LR, et al. A Strong Graded Relationship between Level of Obesity and COPD: Findings from a National Population-Based Study of Life-long Nonsmokers. *Journal of Obesity*, 2018; 6149263. doi: 10.1155/2018/6149263.
61. Asghar A, Sheikh N. Role of immune cells in obesity induced low grade inflammation and insulin resistance. *Cellular Immunology*, 2017; 315, 18-26. doi: 10.1016/j.cellimm.2017.03.001.
62. Rojas-Osornio SA, Cruz-Hernández TR, Drago-Serrano ME, Campos-Rodríguez R. Immunity to influenza: Impact of obesity. *Obesity Research and Clinical Practice*, 2019; 13 (5), 419-429. doi: 10.1016/j.orcp.2019.05.003.
63. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*, 2020; 395 (10229), 1033-1034. doi: 10.1016/S0140-6736(20)30628-0.
64. Guo R, Zheng Y, Yang J, Zheng N. Association of TNF-alpha, IL-6 and IL-1beta gene polymorphisms with polycystic ovary syndrome: a meta-analysis. *BMC Genetics*, 2015; 16 (1), 5. doi: 10.1186/s12863-015-0165-4.

65. Muscogiuri G, Pugliese G, Barrea L, et al. Commentary: Obesity: The “Achilles heel” for COVID-19? *Metabolism*. 2020; 108, 154251. doi: 10.1016/j.metabol.2020.154251.
66. Zeng Q, Li YZ, Huang G, Wu W, Dong SY, Xu Y, et al. Mortality of COVID-19 is associated with cellular immune function compared to immune function in Chinese han population. *MedRxiv*.
67. Huang R, Zhu L, Xue L, et al. Clinical findings of patients with coronavirus disease 2019 in Jiangsu province, China: A retrospective, multi-center study. *PLoS Neglected Tropical Disease*. 2020; 14 (5), e0008280. doi: 10.1371/journal.pntd.0008280.
68. Alpdemir M, Alpdemir MF. Meta Analysis Vitamin D deficiency status in Turkey: A meta-analysis. *Int Journal of Medical Biochemistry*, 2019; 2 (3),118-31.
69. Holick MF. Vitamin D deficiency. *New England Journal of Medicine*, 2007; 357 (3), 266-81. doi: 10.1056/NEJMra070553.
70. Thomson RL, Spedding S, Buckley JD. Vitamin D in the aetiology and management of polycystic ovary syndrome. *Clinical Endocrinology (Oxf)*. 2012; 77 (3), 343-50. doi: 10.1111/j.1365-2265.2012.04434.x. PMID: 22574874.
71. Menichini D, Facchinetti F. Effects of vitamin D supplementation in women with polycystic ovary syndrome: a review. *Gynecological Endocrinology*, 2020; 36 (1), 1-5. doi: 10.1080/09513590.2019.1625881.
72. Muscogiuri G, Mitri J, Mathieu C, et al. Mechanisms in endocrinology: vitamin D as a potential contributor in endocrine health and disease. *European Journal of Endocrinology*, 2014; 171 (3), R101-10. doi: 10.1530/EJE-14-0158.
73. Reis GV, Gontijo NA, Rodrigues KF, et al. Vitamin D receptor polymorphisms and the polycystic ovary syndrome: A systematic review. *Journal of Obstetrics and Gynaecology Research*, 2017; 43 (3), 436-446. doi: 10.1111/jog.13250.
74. Azadi-Yazdi M, Nadjarzadeh A, Khosravi-Boroujeni H, et al. The Effect of Vitamin D Supplementation on the Androgenic Profile in Patients with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Clinical Trials. *Hormone and Metabolic Research*, 2017; 49 (3), 174-179. doi: 10.1055/s-0043-103573.
75. Akbari M, Ostadmohammadi V, Lankarani KB, et al. The Effects of Vitamin D Supplementation on Biomarkers of Inflammation and Oxidative Stress Among Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Hormone and Metabolic Research*, 2018; 50 (4), 271-279. doi: 10.1055/s-0044-101355.
76. Miao CY, Fang XJ, Chen Y, et al. Effect of vitamin D supplementation on polycystic ovary syndrome: A meta-analysis. *Experimental and Therapeutic Medicine*, 2020; 19 (4), 2641-2649. doi: 10.3892/etm.2020.8525.
77. Grant WB, Lahore H, McDonnell SL, et al. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients*, 2020; 12 (4), 988. doi: 10.3390/nu12040988.
78. Lagunova Z, Porojnicu AC, Lindberg F, et al. The dependency of vitamin D status on body mass index, gender, age and season. *Anticancer Research*. 2009; 29 (9), 3713-20.
79. Wortsman J, Matsuoka LY, Chen TC, et al. Decreased bioavailability of vitamin D in obesity. *American Journal of Clinical Nutrition*, 2000; 72 (3), 690-3. doi: 10.1093/ajcn/72.3.690. Erratum in: *American Journal of Clinical Nutrition*,. 2003; 77(5):1342.
80. Silberstein M. Vitamin D: A simpler alternative to tocilizumab for trial in COVID-19? *Medical Hypotheses*. 2020; 140, 109767. doi: 10.1016/j.mehy.2020.109767.
81. Tian Y, Rong L. Letter: Covid-19, and vitamin D. Authors’ reply. *Alimentary Pharmacology and Therapeutics*, 2020; 51 (10), 995-996. doi: 10.1111/apt.15764.
82. Marik PE, Kory P, Varon J. Does vitamin D status impact mortality from SARS-CoV-2 infection? *Medicine in Drug Discovery*. 2020; 6:100041. doi: 10.1016/j.medidd.2020.100041.
83. Mohan M, Cherian JJ, Sharma A. Exploring links between vitamin D deficiency and COVID-19. *PLoS Pathogens*, 2020; 16 (9), e1008874. doi: 10.1371/journal.ppat.1008874.

84. Helming L, Böse J, Ehrchen J, et al. 1alpha,25-Dihydroxyvitamin D3 is a potent suppressor of interferon gamma-mediated macrophage activation. *Blood*, 2005;106(13):4351-8. doi: 10.1182/blood-2005-03-1029.
85. Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging Clinical and Experimental Research*, 2020; 32 (7), 1195-1198. doi: 10.1007/s40520-020-01570-8.
86. Escobar-Morreale HF. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. *Nature Reviews Endocrinology*, 2018; 14 (5), 270-284. doi: 10.1038/nrendo.2018.24.
87. Taniguchi CM, Emanuelli B, Kahn CR. Critical nodes in signalling pathways: insights into insulin action. 2006;7 (2), 85-96. doi: 10.1038/nrm1837. PMID: 16493415.
88. Dror E, Dalmás E, Meier DT, et al. Postprandial macrophage-derived IL-1 β stimulates insulin, and both synergistically promote glucose disposal and inflammation. *Nature Immunology*. 2017; 18 (3), 283-292. doi: 10.1038/ni.3659.
89. Tsai S, Clemente-Casares X, Zhou AC, et al. Insulin Receptor-Mediated Stimulation Boosts T Cell Immunity during Inflammation and Infection. *Cell Metabolism*, 2018 Dec 4; 28 (6): 922-934. e4. doi: 10.1016/j.cmet.2018.08.003.
90. Pearson-Stuttard J, Blundell S, Harris T, et al. Diabetes and infection: assessing the association with glycaemic control in population-based studies. *Lancet Diabetes & Endocrinology*, 2016; 4 (2), 148-58. doi: 10.1016/S2213-8587(15)00379-4.
91. Li S, Wang J, Zhang B, et al. Diabetes Mellitus and Cause-Specific Mortality: A Population-Based Study. *Diabetes & Metabolism Journal*, 2019; 43 (3), 319-341. doi: 10.4093/dmj.2018.0060.
92. Knapp S. Diabetes and infection: is there a link?--A mini-review. *Gerontology*, 2013; 59 (2), 99-104. doi: 10.1159/000345107.
93. Hussain A, Bhowmik B, do Vale Moreira NC. COVID-19 and diabetes: Knowledge in progress. *Diabetes Research and Clinical Practice*, 2020; 162, 108142. doi: 10.1016/j.diabres.2020.108142.
94. Moutschen MP, Scheen AJ, Lefebvre PJ. Impaired immune responses in diabetes mellitus: analysis of the factors and mechanisms involved. Relevance to the increased susceptibility of diabetic patients to specific infections. *Diabete & Metabolisme*, 1992; 18 (3), 187-201.
95. Kohio HP, Adamson AL. Glycolytic control of vacuolar-type ATPase activity: a mechanism to regulate influenza viral infection. *Virology*, 2013; 444 (1-2), 301-9. doi: 10.1016/j.virol.2013.06.026.
96. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. *Cell*, 2014; 157 (1), 121-41. doi: 10.1016/j.cell.2014.03.011.
97. Ottman N, Smidt H, de Vos WM, et al. The function of our microbiota: who is out there and what do they do? *Frontiers in Cellular and Infection Microbiology*, 2012; 2, 104. doi: 10.3389/fcimb.2012.00104.
98. Waldor MK, Tyson G, Borenstein E, et al. Where next for microbiome research? *PLoS Biology*, 2015; 13 (1), e1002050. doi: 10.1371/journal.pbio.1002050.
99. Kalantar-Zadeh K, Ward SA, Kalantar-Zadeh K, et al. Considering the Effects of Microbiome and Diet on SARS-CoV-2 Infection: Nanotechnology Roles. *ACS NANO*, 2020; 14 (5), 5179-5182. doi: 10.1021/acsnano.0c03402.
100. Mak JWY, Chan FKL, Ng SC. Probiotics and COVID-19: one size does not fit all. 2020; 5 (7), 644-645. doi: 10.1016/S2468-1253(20)30122-9.
101. Li N, Ma WT, Pang M, et al. The Commensal Microbiota and Viral Infection: A Comprehensive Review. *Frontiers in Immunology*, 2019; 10, 1551. doi: 10.3389/fimmu.2019.01551.
102. Ghosh SS, Wang J, Yannie PJ, et al. Intestinal Barrier Dysfunction, LPS Translocation, and Disease Development. *Journal of the Endocrine Society*, 2020; 4 (2), bvz039. doi: 10.1210/jendso/bvz039.
103. Liang Y, Ming Q, Liang J, et al. Gut microbiota dysbiosis in polycystic ovary syndrome: association with obesity - a preliminary report. *Canadian Journal of Physiology and Pharmacology*, 2020; 98 (11), 803-809. doi: 10.1139/cjpp-2019-0413.