

Bölüm 32

KRONİK PANKREATİT

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GİRİŞ

Kronik pankreatit, pankreas bezinin fibro-inflamatuar bir hastalığı olup , asiner ve adacık hücrelerinin kaybıyla seyreden progresif bir hastalıktır(1). Tekrarlayan inflamasyonlar sonrası gelişen hücre kaybı, pankreasın endokrin ve ekzokrin fonksiyonlarında yetmezliğe neden olmaktadır(2). Hastalık genel olarak karın ağrısı, endokrin ve ekzokrin yetmezlik, son olarak da ikincil pankreas kanseri şeklinde prezente olabilir(3). Erken evrelerinde tekrarlayan akut pankreatit atakları ve karın ağrısı gözlenirken, ileri dönemlerde, skleroz, kalsifikasyon, diyabetes mellitus, steatore gibi bulgular karşımıza çıkmaktadır.

Epidemiyoloji

Kronik pankreatitin yaygınlığına dair az sayıda çalışma bulunması nedeniyle elimizdeki veriler çoğunlukla büyük merkezlerdeki kaytlardan oluşmaktadır. Bununla beraber kronik pankreatit Avrupa ve Amerika Birleşik Devletleri'nde (ABD) hala önemli bir ölüm sebebidir (4). ABD'de yıllık insidans 100000'de 4.4-11.9 arasında değişmekte olup, prevalansı 100000'de 36.9-41.8 arasında değişmektedir(5-6). Bununla birlikte hastalığın daha anlaşılır hale gelmesi ve ortalama yaşam süresinin 15-20 yıl gibi uzun olması nedeniyle prevalansın 100000'de 120-143 arasında değiştiğini ifade eden çalışmalar vardır (7).

Etyoloji ve Risk Faktörleri

Kronik pankreatitin tipik morfolojisi inflamasyon, kalsiyum depozitleri, pankreatik kanalda değişiklikler veya psödokist şeklindedir. Hastaların çoğunluğu erkek olup 5. veya 6. dekatta tanı alırlar . Hastalığın etyolojisi genel olarak alkol, genetik, hiperlipidemi ve idyopatik olarak sınıflandırılmaktadır (3). En sık etken ise alkol kullanımı olup, batı toplumlarında tüm vakaların yaklaşık %40-70'i alkol kaynaklıyken Japonyada da benzer oranlar saptanmıştır. (8-9-10). Kadınlarda alkol kaynaklı kronik pankreatit sadece %28 oranında olup, idiyopatik nedenler ön plana çıkmaktadır(11)Hastaların birçoğunda birden fazla etyolojik faktörün bulunduğu görülmüştür. Riska faktörleri TIGAR-O (The Toxic-Metabolic, Idiopathic, Genetic, Autoimmun, Recurrent and Severe Acute Pancreatitis) sistemi ile sınıflandırılmış olup, bir veya birden fazla risk faktörünün hangi mekanizma ile kronik pankreatite neden olduğunu anlamamız yardımcı olur(Tablo1).

Risk Faktörleri

Alkol

Tüm kronik pankreatitlerin yaklaşık %65 i alkol kaynaklıyken , hastalığın alkol dozu ile ilişkisi saptanmıştır.Alkolün etkisi doz bağımlı olup, kadınlarda düşük dozlarda alkol alımına rağmen riskin daha fazla olduğu gözlenmiştir.NAPS2 çalışmasına göre günlük alkollü içecek tüketimi 5'in üzerinde olan kişilerde (60-80 gr etanol) kronik

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KAYNAKLAR

1. *Opinion in Gastroenterology*, 33(5), 396–403. doi:10.1097/mog.0000000000000377
2. Patel, V., & Willingham, F. (2019). *The Management of Chronic Pancreatitis. Medical Clinics of North America*, 103(1), 153–162. doi:10.1016/j.mcna.2018.08.012
3. Pham, A., & Forsmark, C. (2018). *Chronic pancreatitis: review and update of etiology, risk factors, and management. F1000Research*, 7, 607. doi:10.12688/f1000research.12852.1
4. Whitcomb, D. C. et al. Chronic pancreatitis: an international draft consensus proposal for a new mechanistic definition. *Pancreatology* 16, 218–224 (2016).
5. Lankisch PG, Assmus C, Maisonneuve P, et al. Epidemiology of pancreatic diseases in Luneburg County. A study in a defined German population. *Pancreatology* 2002;2:469–77
6. Yadav D, Timmons L, Benson JT, et al. Incidence, prevalence, and survival of chronic pancreatitis: a population-based study. *Am J Gastroenterol* 2011; 106:2192–9.
7. Levy, P., Dominguez-Munoz, E., Imrie, C., Lohr, M. & Maisonneuve, P. Epidemiology of chronic pancreatitis: burden of the disease and consequences. *United European Gastroenterol. J.* 2, 345–354 (2014).
8. Hirota, M. et al. The seventh nationwide epidemiological survey for chronic pancreatitis in Japan: clinical significance of smoking habit in Japanese patients. *Pancreatology* 14, 490–496 (2014).
9. Masamune, A. et al. Nationwide epidemiological survey of early chronic pancreatitis in Japan. *J. Gastroenterol.* 52, 992–1000 (2017).
10. Cote, G. A. et al. Alcohol and smoking as risk factors in an epidemiology study of patients with chronic pancreatitis. *Clin. Gastroenterol. Hepatol.* 9, 266–273 (2011).
11. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology* 2013;144:1252-61. 10.1053/j.gastro.2013.01.068 23622135
12. Yang, A. L., Vadhavkar, S., Singh, G. & Omary, M. B. Epidemiology of alcohol-related liver and pancreatic disease in the United States. *Arch. Intern. Med.* 168, 649–656 (2008).
13. Pandolfi SJ, Gorelick FS, Gerloff A, et al.: Alcohol abuse, endoplasmic reticulum stress and pancreatitis. *Dig Dis.* 2010; 28(6): 776–82.
14. Kleeff, J., Whitcomb, D. C., Shimosegawa, T., Esposito, I., Lerch, M. M., Gress, T., ... Neoptolemos, J. P. (2017). *Chronic pancreatitis. Nature Reviews Disease Primers*, 3, 17060. doi:10.1038/nrdp.2017.60
15. Whitcomb DC, LaRusch J, Krasinskas AM, et al.: Common genetic variants in the CLDN2 and PRSS1-PRSS2 loci alter risk for alcohol-related and sporadic pancreatitis. *Nat Genet.* 2012; 44(12): 1349–54
16. Yadav D, Hawes RH, Brand RE, et al.: Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. *Arch Intern Med.* 2009; 169(11): 1035–45
17. Yadav, D. & Whitcomb, D. C. The role of alcohol and smoking in pancreatitis. *Nat. Rev. Gastroenterol. Hepatol.* 7, 131–145 (2010).
18. Rebours, V. et al. The natural history of hereditary pancreatitis: a national series. *Gut* 58, 97–103 (2009).
19. Masamune, A. Genetics of pancreatitis: the 2014 update. *Tohoku J. Exp. Med.* 232, 69–77 (2014).
20. Weiss, F. U., Skube, M. E., & Lerch, M. M. (2018). *Chronic pancreatitis. Current Opinion in Gastroenterology*, 1. doi:10.1097/mog.0000000000000461
21. Whitcomb DC, Gorry MC, Preston RA, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. *Nat Genet* 1996; 14:141–145.
22. Noone, P. G. et al. Cystic fibrosis gene mutations and pancreatitis risk: relation to epithelial ion transport and trypsin inhibitor gene mutations. *Gastroenterology* 121, 1310–1319 (2001).
23. Schneider, A. et al. Combined bicarbonate conductance-impairing variants in CFTR and SPINK1 variants are associated with chronic pancreatitis in patients without cystic fibrosis. *Gastroenterology* 140, 162–171 (2011).
24. Tadenuma H, Ishihara T, Yamaguchi T, et al.: Long-term results of extracorporeal shockwave lithotripsy and endoscopic therapy for pancreatic stones. *Clin Gastroenterol Hepatol.* 2005; 3(11): 1128–35.
25. Bülow R, Simon P, Thiel R, et al.: Anatomic variants of the pancreatic duct and their clinical relevance: an MR-guided study in the general population. *Eur Radiol.* 2014; 24(12): 3142–9.
26. Witt H, Apte MV, Keim V, et al. Chronic pancreatitis: challenges and advances in pathogenesis, genetics, diagnosis, and therapy. *Gastroenterology* 2007; 132:1557–1573
27. Apte MV, Pirola RC, Wilson JS. Pancreatic stellate cells: a starring role in normal and diseased pancreas. *Front Physiol* 2012; 3:344
28. Emmrich J, Weber I, Nausch M, et al. Immunohistochemical characterization of the pancreatic cellular infiltrate in normal pancreas, chronic pancreatitis and pancreatic carcinoma. *Digestion* 1998; 59:192–198.
29. Deng X, Wang L, Elm MS, et al. Chronic alcohol consumption accelerates fibrosis in response to cerulein-induced pancreatitis in rats. *Am J Pathol* 2005; 166:93–106.
30. Kloppel, G. & Maillet, B. Pseudocysts in chronic pancreatitis: a morphological analysis of 57 resection specimens and 9 autopsy pancreata. *Pancreas* 6, 266–274 (1991)
31. Bhanot, U. K. & Moller, P. Mechanisms of parenchymal injury and signaling pathways in ectatic ducts of chronic pancreatitis: implications for pancreatic carcinogenesis. *Lab. Invest.* 89, 489–497 (2009).
32. Leung, P. S. & Chan, Y. C. Role of oxidative stress in pancreatic inflammation. *Antioxid. Redox Signal.* 11, 135–165 (2009).

33. Kloppel G. Chronic pancreatitis, pseudotumors and other tumor-like lesions. *Mod Pathol* 2007;20(Suppl 1):S113–31.
34. Stram, M., Liu, S., & Singhi, A. D. (2016). Chronic Pancreatitis. *Surgical Pathology Clinics*, 9(4), 643–659. doi:10.1016/j.path.2016.05.008
35. Kamisawa T, Funata N, Hayashi Y, et al. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003;38:982–4
36. Chowdhury RS, Forsmark CE: Review article: Pancreatic function testing. *Aliment Pharmacol Ther*. 2003; 17(6): 733–50.
37. Lindkvist B: Diagnosis and treatment of pancreatic exocrine insufficiency. *World J Gastroenterol*. 2013; 19(42): 7258–66.
38. Domínguez-Muñoz JE, Iglesias-García J, Iglesias-Rey M, et al.: Effect of the administration schedule on the therapeutic efficacy of oral pancreatic enzyme supplements in patients with exocrine pancreatic insufficiency: a randomized, three-way crossover study. *Aliment Pharmacol Ther*. 2005; 21(8): 993–1000.
39. Rousselot Lm, Sanchez-Ubeda R, Giannelli S: Cholecystochoenterostomy in chronic relapsing pancreatitis; a study of five case
40. Sikkens EC, Cahen DL, Koch AD, et al.: The prevalence of fat-soluble vitamin deficiencies and a decreased bone mass in patients with chronic pancreatitis. *Pancreatolgy*. 2013; 13(3): 238–42.
41. Tirkes, T. (2018). *Chronic Pancreatitis. Magnetic Resonance Imaging Clinics of North America*, 26(3), 451–461. doi:10.1016/j.mric.2018.03.012
42. Olesen, S. S. et al. Pain severity reduces life quality in chronic pancreatitis: implications for design of future outcome trials. *Pancreatolgy* 14, 497–502 (2014).
43. Rickels, M. R. et al. Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: recommendations from PancreasFest 2012. *Pancreatolgy* 13, 336–342 (2013). A comprehensive review and recommendations for evaluating and managing diabetes mellitus in patients with chronic pancreatitis
44. Layer P, Yamamoto H, Kalthoff L, et al. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. *Gastroenterology* 1994; 107(5):1481–7.
45. Mergener K, Baillie J. Chronic pancreatitis. *Lancet* 1997;350(9088):1379–85.
46. Amann ST, Bishop M, Curington C, Toskes PP. Fecal pancreatic elastase 1 is inaccurate in the diagnosis of chronic pancreatitis. *Pancreas* 1996; 13:226– 230.
47. Keim V, Teich N, Moessner J. Clinical value of a new fecal elastase test for detection of chronic pancreatitis. *Clin Lab* 2003;49(5–6):209–15.
48. Wejnarska K, Kolodziejczyk E, Ryzko J, Oracz G. Comparison of 72-hour fecal fat quantification and the 13C-mixed triglyceride breath test in assessing pancreatic exocrine sufficiency in children with chronic pancreatitis. *Dev Period Med* 2016; 20:222–227.
49. Bolondi L, Li Bassi S, Gaiani S, et al. Sonography of chronic pancreatitis. *Radiol Clin North Am* 1989; 27(4):815–33.
50. Catalano MF, Sahai A, Levy M, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. *Gastrointest Endosc* 2009; 69:1251–1261.
51. Rana SS, Vilmann P. Endoscopic ultrasound features of chronic pancreatitis: a pictorial review. *Endosc Ultrasound* 2015; 4:10–14.
52. Rickes S, Monkemuller K, Malferteiner P. Contrast-enhanced ultrasound in the diagnosis of pancreatic tumors. *JOP* 2006; 7:584–592.
53. Chey WY, Chang TM. Secretin: historical perspective and current status. *Pancreas* 2014; 43:162–182.
54. Tirkes T, Fogel EL, Sherman S, et al. Detection of exocrine dysfunction by MRI in patients with early chronic pancreatitis. *Abdom Radiol (NY)* 2017; 42:544– 551.
55. Sandrasegaran K, Tahir B, Barad U, et al. The value of secretin-enhanced MRCP in patients with recurrent acute pancreatitis. *AJR Am J Roentgenol* 2017; 208:315–321.
56. Schneider A, Lohr JM, Singer MV. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease. *J Gastroenterol* 2007;42(2):101–19.
57. Mullady DK, Yadav D, Amann ST, et al. NAPS2 Consortium. Type of pain, pain-associated complications, quality of life, disability and resource utilisation in chronic pancreatitis: a prospective cohort study. *Gut* 2011;60:77–84. 10.1136/gut.2010.213835 21148579
58. Delhay, M. et al. Belgian consensus on chronic pancreatitis in adults and children: statements on diagnosis and nutritional, medical, and surgical treatment. *Acta Gastroenterol. Belg.* 77, 47–65 (2014).
59. Lapp RT, Wolf JS, Faerber GJ, et al. Duct diameter and size of stones predict successful extracorporeal shock wave lithotripsy and endoscopic clearance in patients with chronic pancreatitis and pancreaticolithiasis. *Pancreas* 2016; 45:1208–1211.
60. Ashkar M, Gardner TB. Role of endoscopic ultrasound in pancreatic diseases: a systematic review. *Minerva Gastroenterol Dietol* 2014;60:227–45.25288203
61. Forsmark CE. Management of chronic pancreatitis. *Gastroenterology* 2013; 144(6):1282–91.
62. Jadad, A. R. & Browman, G. P. The WHO analgesic ladder for cancer pain management. Stepping up the quality of its evaluation. *JAMA* 274, 1870–1873 (1995).
63. Drewes, A. M. et al. Differences between opioids: pharmacological, experimental, clinical and economical perspectives. *Br. J. Clin. Pharmacol.* 75, 60–78 (2013)
64. Moran RA, James T, Pasricha PJ. Pancreatic pain. *Curr Opin Gastroenterol* 2015;31:407–15. 10.1097/MOG.000000000000204 26154428
65. Olesen SS, Bouwense SA, Wilder-Smith OH, van Goor H, Drewes AM. Pregabalin reduces pain in patients

- with chronic pancreatitis in a randomized, controlled trial. *Gastroenterology* 2011;141:536-43. 10.1053/j.gastro.2011.04.003 21683078
66. Hall TC, Garcea G, Webb MA, et al.: The socio-economic impact of chronic pancreatitis: a systematic review. *J Eval Clin Pract.* 2014; 20(3): 203–7.
67. Duggan SN, Smyth ND, Murphy A, Macnaughton D, O’Keefe SJ, Conlon KC. High prevalence of osteoporosis in patients with chronic pancreatitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2014;12:219-28. 10.1016/j.cgh.2013.06.016 23856359
68. Toouli J, Biankin AV, Oliver MR, et al.: Management of pancreatic exocrine insufficiency: Australasian Pancreatic Club recommendations. *Med J Aust.* 2010; 193(8): 461–7.
69. Rickels MR, Bellin M, Toledo FG, etal. PancreasFest Recommendation Conference Participants. Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: recommendations from PancreasFest 2012. *Pancreatology* 2012;13:336-42. 10.1016/j.pan.2013.05.002 23890130
70. Andersen DK, Andren-Sandberg Å, Duell EJ, et al.: Pancreatitis-diabetopancreatic cancer: summary of an NIDDK-NCI workshop. *Pancreas.* 2013; 42(8): 1227–37