

METABOLİK ACİDAN HİPERLİPİDEMİ

Arzu GÜNTÜRK¹

Giriş

Hiperlipidemi primer ve sekonder olarak 2 başlıkta toplanabilir. Primer hiperlipidemi genetik nedenlidir. Ailevi dislipidemiler primer hiperlipidemi sebebidirler. Sekonder hiperlipidemi ise alatta yatan hastalıklar sonucu ortaya çıkar (1). Çevresel faktörler (diyet, alkol kullanımı), diabet, obezite, metabolik sendrom, hipotiroidi, kronik böbrek yetmezliği, nefrotik sendrom, kronik karaciğer hastalığı, kolestaz ve ilaçlara bağlı olarak sekonder hiperlipidemi görülebilir (2). Lipidler hem vücudumuzda üretilir, hem dışarıdan alınırlar.

Kan lipidleri trigliseridler, lipoproteinler, fosfolipidler, kolesterol ve serbest yağ asitlerinden oluşur. Kandaki kolesterol ve trigliseridler lipoproteinler şeklinde taşınırlar. Protein fraksiyonu fazla olan kısım yüksek dansiteli lipoprotein (HDL), az olan kısım ise düşük dansiteli lipoprotein (LDL) olarak adlandırılır. Kandaki total lipidin %25'ini trigliserid, 1/3'ünü ise kolesterol oluşturur. Lipidler vücudun %10'unu oluşturur. Bu nün çoğunuğu trigliseriddir. Trigliseridler yağ dokusunda daha çok bu-

¹ Dr. Öğr. Üyesi, Yeditepe Üniversitesi İç Hastalıkları AnaBilim Dalı
arzu.gunturk@yeditepe.edu.tr

Yine KBY'likli hastalarda atherogenik lipoprotein partikülü olan Lp(a) nin plazma konsantrasyonu artmıştır. Mekanizma çok net olmakla birlikte azalmış klirensle ilişkili olduğu düşünülmektedir.

Kolestaz ve Lipid Metabolizması

Safra kesesi ve safra yolları hastalıklarında hiperlipidemi değişken olarak görülebilir. Biliyer obstrüksiyonda en fazla görülür. En önemli mekanizma safra asitlerinin (ve olasılıkla kolesterolün) safra kesesine ekskresyonunun bozulmasıdır. Safra asidi düzeyleri kanda yükselir, kolesterolün karaciğerde safra asitlerine dönüşümü azalır. Lesitin kolesterol aciltransferaz (LCAT) azalır. LCAT enzimi yağ asitlerini kolesterol esteri ve lizofosfatidil koline dönüştürür. LCAT düzeyi düşüklüğü, anomal diskoid HDL partikülleri oluşumuna neden olur.

Sonuç

Lipid metabolizması, hücrelerde enerji oluşumunun önemli bir öğesidir. Karbonhidrat ve protein metabolizmasıyla da ilişkilidir. Lipid metabolizması bozuklukları, doğrudan aterosklerotik hastalıklarla ilişkilidir. Bu nedenle lipit metabolizmasını bozacak ek hastalıklar önemsenmeli ve zamanında tedavilerinin planlanması gerekmektedir.

Kaynaklar

1. Rini BI, Wilding G, Hudes G, et al. Phase II study of axitinib in sorafenib refractory metastatic renal cell carcinoma. *J Clin Oncol.* 2009; 27:444-448.
2. Duell PB, Illingworth DR, Connor WE. (2001). Secondary Hyperlipidemias. Felig P, Frohman LA(Ed.) *Endocrinology & Metabolism* içinde (1009-1013). USA: McGraw-Hill
3. Cobbina E and Akhlaghi F. Non-Alcoholic Fatty Liver Disease (NAFLD)-Pathogenesis, Classification, and Effect of Drug Metabolizing Enzymes and Transporters. *Drug Metab Rev.* 2017 May; 49(2): 197-211.
4. Jiang W, Wu N, Wang X, et al. Dysbiosis gut microbiota associated with inflammation and impaired mucosal immune function in intestine of humans with non-alcoholic fatty liver disease. *Sci Rep.* 2015; 5:8096.
5. Kirpich IA, Marsano LS, McClain CJ. Gut-liver axis, nutrition, and non-alcoholic fatty liver disease. *Clin Biochem.* 2015; 48:923-30.

6. Romeo S, Kozlitina J, Xing C, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet.* 2008; 40:1461–5.
7. Anderson N, Borlak J. Molecular mechanisms and therapeutic targets in steatosis and steatohepatitis. *Pharmacol Rev.* 2008; 60:311–57.
8. Greco D, Kotronen A, Westerbacka J, et al. Gene expression in human NAFLD. *Am J Physiol Gastrointest Liver Physiol.* 2008; 294: G1281–7.
9. Fabbrini E, Magkos F, Mohammed B, et al. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. *PNAS.* 2009; 106:15430–5.
10. Browning J, Horton J. Molecular mediators of hepatic steatosis and liver injury. *J Clin Invest.* 2004; 114:147–52.
11. Bell M, Wang H, Chen H, et al. Consequences of lipid droplet coat protein downregulation in liver cells: abnormal lipid droplet metabolism and induction of insulin resistance. *Diabetes.* 2008; 57:2037–45.
12. Sanyal AJ, Friedman SL, McCullough AJ, et al. Challenges and opportunities in drug and biomarker development for nonalcoholic steatohepatitis: Findings and recommendations from an American Association for the Study of Liver Diseases–U.S. Food and Drug Administration Joint Workshop. *Hepatology.* 2015; 61:1392–1405.
13. Tiniakos D, Vos M, Brunt E. Nonalcoholic fatty liver disease: pathology and pathogenesis. *Annu Rev Pathol.* 2010; 5:145–71.
14. Ramadori G, Armbrust T. Cytokines in the liver. *Eur J Gastroenterol Hepatol.* 2001; 13:777–84.
15. Joshi-Barve S, Barve S, Amacherla K, et al. Palmitic acid induces production of proinflammatory cytokine interleukin-8 from hepatocytes. *Hepatology.* 2007; 46:823–30.
16. National diabetes fact sheet. Center for Disease Control, Prevention. Accessed at http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf(2011)
17. Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* 24 (2008), pp.2545-59.
18. Betteridge DJ. Diabetic dyslipidaemia-implications for vascular risk. In: Betteridge DJ, ed. *Lipids: Current Perspectives.* London: Martin Dunitz 1996: 135-57.
19. Behar S, Benderly M, Reicher-Reiss H, et al. for the Bezafibrate Infarction Prevention (BIP) Study. Lipid Profile and outcome of diabetic patients with coronary artery disease in the BIP Study Registry. Abstract presented at American College of Cardiology, March 1997 Anaheim, California.
20. Jorgensen AB, Frikkie-Schmidt, Nordestgaard BG, et al. Loss of function mutations in APOC3 and risk of ischemic vascular disease. *N Engl J Med.* 371(1) (2014), pp.32-41.
21. Duez H, Lamarche B, Uffelman KD, et al. Hyperinsulinemia is associated with increased production rate of intestinal apolipoprotein B-48-containing lipoproteins in humans. *Arterioscler Thromb Vasc Biol.* 26(6) (2006), pp.1357-63.
22. Hogue JC, Lamarche B, Tremblay AJ, et al. Evidence of increased secretion of apolipoprotein B-48-containing lipoproteins in subjects with type 2 diabetes. *J Lipid Res.* 48(6) (2007), pp.1336-42.
23. Cowie CC, Howard BV, Harris MI, Serum lipoproteins in African Americans and whites with non-insulin-dependent diabetes in the US population. *Circulation.* 90 (3) (1994), pp.1185-93.
24. Austin MA, Edwards KL. Small, dense low density lipoproteins, the insulin resistance syndrome and noninsulin-dependent diabetes. *Curr Opin Lipidol.* 7 (3) (1996), pp.167-71.
25. Carmena R, Duriez P, Fruchart JC. Atherogenic lipoprotein particles in atherosclerosis. *Circulation.* 109 (23 Suppl 1) (2004), pp.1112-17.

26. Campbell MC, Anderson GW, Mariash CN. Human spot 14 glucose and thyroid hormone response characterization and thyroid hormone response element identification. *Endocrinology*. 2003; 144: 5242-48.
27. Desvergne B, Petty KJ, Nikodem VM. Functional characterization and receptor binding studies of the malic enzyme thyroid hormone response element. *J Biol Chem*. 1991; 266:1008-13.
28. Zhang Y, Yin L, Hillgartner FB. Thyroid hormone stimulates acetyl-coA carboxylase- α transcription in hepatocytes by modulating the composition of nuclear receptor complexes bound to a thyroid hormone response element. *J Biol Chem*. 2001; 276: 974-83.
29. Radenne A, Akpa M, Martel C, et al. Hepatic regulation of fatty acid synthase by insulin and T3: evidence for T3genomic and nongenomic actions. *Am J Physiol Endocrinol Metab*. 2008; E884-94.
30. Brenta G, Berg G, Miksztowicz V, et al. Atherogenic lipoproteins in subclinical hypothyroidism and their relationship with hepatic lipase activity: response to replacement treatment with levothyroxine. *Thyroid*. 2016; 26: 365-72.
31. Singh R, Kaushik S, Wang Y, et al. Autophagia regulates lipid metabolism. *Nature*. 2009; 458: 1131-35.
32. Cingolani F, Czaja MJ. Regulation and functions of autophagic lipolysis. *Trends Endocrinol Metab*. 2016; 27: 696-705.
33. Sinha RA, You SH, Zhou J, et al. Thyroid hormone stimulates hepatic lipid catabolism via activation of autophagy. *J Clin Invest*. 2012; 122: 2428-38.
34. Glueck C, Lang J, Tracy T, et al. High prevalence of hypothyroidism in patients with hyperlipoproteinemia. *Clin Chim Acta* 201: 113, 1991.
35. Illingworth DR, Griffiths D, Thorogood M: Asymptomatic hypothyroidism in hypercholesterolemic patients. *JR Soc Med* 84: 527, 1991.
36. Wu J, Zhu YH, Patel SB: Cyclosporin-induced dyslipoproteinemia is associated with selective activation of SREBP-2. *Am J Physiol* 277(6 pt 1): E1087,1999.