

OBEZİTE VE UYKU APNESİ

10. BÖLÜM

Mustafa ÖZMAN¹

Giriş

Vücuda alınan enerjinin harcanan enerjiden fazla olması durumunda ortaya çıkan obezite, kadınlarda vücut yağ oranının %30'un, erkeklerde %25'in üzerinde olmasıdır. Hastalığın tanı ve takibinde vücut yağ oranına ek olarak BMI (beden kitle indeksi) ve bel çevresi ölçümleri kullanılır.

Obezite, başta kardiyovasküler hastalıklar olmak üzere, diyabet, üreme bozuklukları, osteoartrit, gastrointestinal hastalıklar, respiratuvar hastalıklar, uyku bozuklukları, psikolojik sorunlar ve bazı kanser türleri ile ilişkisi saptanan; dünya genelinde sıklığı giderek artıp, ciddi morbidite ve mortaliteye neden olabilen bir hastalıktır. Global bir halk sağlığı sorunu olan obezite, günümüzde çocuklar ve yetişkinler için tehlikeli sınırlara ulaşmıştır ve getirdiği morbiditeler düşünüldüğünde gelecek nesiller için giderek artan bir sağlık yüküne yol açacağı öngörülmektedir (1).

“Obstrüktif uyku apnesi (OSA)” ise klinik olarak uyku sırasında aralıklı üst solunum yolu daralması, horlama ve hava akımında azalma ve durmayla karakterize bir hastalıktır. Bu semptomlara gündüz uykululuğu da eşlik ediyorsa o zaman “Obstrüktif uyku apnesi sendromu (OSAS)” olarak isimlendirilir.

Obezite, OSAS (obstrüktif uyku apnesi sendromu) için majör bir risk faktörüdür ve aralarında çift yönlü bir ilişki mevcuttur. Obezite OSAS fizyopatolojisinde rol oynarken, OSAS sonucu gelişen gündüz uykululuk ve azalan fiziksel aktivite ise obezite gelişmesine ve progresyonuna yol açmaktadır. Yetişkin popülasyon-

¹ Kulak Burun Boğaz Uzmanı, Özel Ünye Çakırtepe Hastanesi. E-mail: mustafaozman@gmail.com

Bir başkası da ghrelin hormonudur(mideden salgılanır, iştahı artırır, vücutta leptinin tersi olarak işlev görür). Gece boyunca salgılanan bu hormonun, uyku bozukluğuyla seyreden OSAS gibi hastalıklarda uyku süresinin kısalmasıyla birlikte, üretimi azalıp kişinin kilo alımı kolaylaşır ve hastalığı kötüleşir(127). Reizistin ve visfatin de OSAS-obezite ilişkisinde rolü olduğu yönünde bulguları olan ve biyomarker olarak kullanılma potansiyelleri bulunan diğer hormonlardır(128).

Toplumsal araştırmalarda kısalmış uyku süresi ile kilo fazlalığı arasında ilişki olduğu ortaya konulmuştur. Deneysel uyku süresi kısalığının obeziteden bağımsız olarak metabolik disregülasyon yaptığı bulunmuştur. Bunlar, uyku süresinin vücut ağırlığında ve metabolik-endokrin fonksiyonlarda önemli bir regulatör olduğunu desteklemektedir(129). Hatta prospektif çalışmalarda habitüel horlamanın bile 10 yıllık periyod içinde 2-7 kat artmış tip 2 diyabet riski oluşturduğu bulunmuştur(130).

Ortaya çıkan bu tabloda OBEZİTE-UYKU BOZUKLUĞU-OSAS arasında sıkı bir ilişki olduğu açıktır (25). Anlamli kilo kaybı ile bu bozuklukların hepsinde birden iyileşme olduğunun klinik çalışmalarla desteklenmesi de bunun kanıtıdır (131).

Sonuç olarak obezite ve uyku apnesi arasındaki kompleks çift yönlü ilişkide 'obezite' baskın olan karakterdir ve yaptığı mekanik, biyokimyasal ve nöromusküler değişiklikler aracılığıyla OSAS gelişimine sebep olur. OSAS'ın obeziteye eğilim oluşturmadaki temel neden ise uykuyla ilgili sorunların getirdiği fizyopatolojik (70) ve ruhsal (132,133) değişikliklerdir.

KAYNAKLAR

1. Matson KL, Fallon RM. Treatment of obesity in children and adolescent. J Pediatr Pharmacol Ther 2012; 17(1):45-47
2. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993; 328 (17): 1230 - 1235 .
3. Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men: I. Prevalence and severity. Am J Respir Crit Care Med. 1998; 157 (1): 144 - 148 .
4. Bixler EO, Vgontzas AN, Lin HM, et al. Prevalence of sleep-disordered breathing in women: effects of gender. Am J Respir Crit Care Med. 2001; 163 (3 Pt 1): 608 - 613 .
5. Durán J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. Am J Respir Crit Care Med. 2001; 163 (3 Pt 1): 685 - 689 .
6. Kim J, In K, Kim J, et al. Prevalence of sleep-disordered breathing in middle-aged Korean men and women. Am J Respir Crit Care Med. 2004; 170 (10): 1108 - 1113 .

7. Sharma SK , Kumpawat S , Banga A , Goel A . Prevalence and risk factors of obstructive sleep apnea syndrome in a population of Delhi, India .Chest .2006 ; 130 (1) : 149 - 156 .
8. Alonso-Álvarez ML, Cordero-Guevara JA, et al., for the Spanish Sleep Network. Obstructive sleep apnea in obese community-dwelling children: the NANOS study. *SLEEP* 2014;37(5):943-949.
9. Patel AK, Araujo JF. StatPearls[Internet]. StatPearls Publishing; Treasure Island(FL):Oct 27,2018. Physiology, Sleep Stages[PubMed: 30252388]
10. Miyazaki S, Liu CY, Hayashi Y. Sleep in vertebrate and invertebrate animals, and insight into the function and evolution of sleep. *Neurosci. Res.* 2017 May;118:3-12
11. Nayak CS, Anilkumar AC, StatPearls[Internet]. StatPearls Publishing; Treasure Island(FL):Dec 4,2019. EEG Normal Sleep[PubMed: 30725708]
12. Khan MS, Auad R. The Effects of Insomnia and Sleep Loss on Cardiovascular Disease. *Sleep Med Clin.* 2017 Jun;12(2):167-177.
13. Irwin MR. Sleep and Inflammation: parents and sickness and in health. *Nat. Rev. Immunol.* 2019 Nov;19(11):702-715.
14. Maquet P. The role of sleep in learning and memory. *Science.* 2001 Nov 02;294(5544):1048-52.
15. E. Blackburn, E. Epel, "Telomer Etkisi-Uzun Yaşamının ve Genç Kalmanın Yeni Bilimi", 3. Baskı, Şubat-2018. S.208
16. Jackowska M. et al. "Short Sleep Duration Is Associated with Shorter Telomer Length in Healthy men: Findings from the Whitehall II Cohort Study", *PLOS ONE* 7, no. 10(2012): e47292
17. Li L, et al. Prevalence of sleep disturbances in Chinese university students: a comprehensive meta-analysis. *J Sleep Res.* Jun 2018
18. Sateia MJ. International Classification of Sleep Disorders-Third Edition: Highlight and Modifications. *Chest* 2014 Nov;146(5):1378-94.
19. Gradner MA. Sleep, Health and Society, (Review)*Sleep Med Clin* 2017
20. Chaput JB, Bouchard C, Tremblay A. Change in sleep duration and visceral fat accumulation over 6 years in adults. *Obesity(Silver Spring).* 2014;22(5):E9-E12
21. Shan Z, Ma H, Xie M et al. Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies. *Diabet Care* 2015;38(3):529-37
22. Fairbanks, N.F. (1994). Snoring: An overview with historical perspectives. *Snoring and Obstructive Sleep Apnea, Second Edition.* Ed: Fairbanks NF ve Fujita S. Raven Pres, New York, 1994; 1-16.
23. AASM, Obstructive Sleep Apnea Syndrome. In: *The International Classification of Sleep Disorders Revisited Diagnostic and Coding Manual; 2001*, pp 52-58.
24. Young T, Shahar E, Nieto FJ, et al; for the Sleep Heart Health Study Research Group. Predictors of sleep-disordered breathing in community-dwelling adults. *Arch Intern Med* 2002; 162(8):893–900.
25. Abel R-C, Francisco L-C. Interaction Between Obesity and Obstructive Sleep Apnea. *CHEST, Postgraduate Education Corner*, 137(3), March 2010, 711-19.
26. Laratta CR, Ayas NT, Povitz M, Pendharkar SR. Diagnosis and treatment of obstructive sleep apnea in adults. *CMAJ* 2017;189(48): E1481-E1488
27. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *The Lancet Respiratory Medicine.* 2019;7(8):687–698.

28. Kapur V, Strohl KP, Redline S, et al. Underdiagnosis of sleep apnea syndrome in U.S. communities. *Sleep Breath.*2002;6:49-54
29. Vgontzas A, Tan T, Bixler E, et al. Sleep apnea and sleep disruption in obese patients. *Arch Int Med* 1994;154:1705-11.
30. Youg T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep syndrome in middle-aged man abn womwn. *Sleep* 1997;20:705-6.
31. Redline S, Kump K, Tishler PV, Browner I, Ferrette V. Gender differences in sleep disordered breathing in a community-based sample. *Am J Respir Crit Care Med* 1994; 149(3 Pt 1): 722–726
32. Shahar E, Redline S, Young T, et al; for the Sleep Heart Health Study Research Group. Hormone replacement therapy and sleep-disordered breathing. *Am J Respir Crit Care Med* 2003; 167(9):1186–1192.
33. Patel SR.Obstructive Sleep Apnea.*Ann Intern Med.* 2019 Dec 3;171(11):ITC81-ITC96.
34. Schwartz AR, Patil SP, Laffan AM at al. Obesity and Obstructive Sleep Apnea, Pathogenic Mechanisms and Therapeutic Approaches. *Proc Am Thorac Soc* 2008; vol 5, issue 2, pp 185-92
35. Martikainen K, Partinene M, Urponen H, et al. Natural evolution of snoring: A 5 year follow up study. *Acta Neurol Scand* 1994;90:437-42
36. Whyte KF, Allen MB, Jeffrey AA, et al. Clinical features of apnoea/hypoponea syndrome. *Q J Med* 1989;72:659-66
37. Schlosshan D, Elliott MW. Clinical preservation diagnosis of the obstructive sleep apnoea hypopnoea syndrome. *Thorax* 2004;59:347-52
38. Tkacova R, Darkova Z, Clinical presentation of OSA in adults. *Eur Respir Monogr* 2010; 50: 86-103
39. Türk Toraks Derneği Obstrüktif Uyku Apne Sendromu Tanı ve Tedavi Uzlaşı Raporu, 2012.
40. John MW, *Sleep* 1992 Aug ; 15(4): 376-81
41. Maislin G, Pack AI, Kribbs NB et al. A survey screen for prediction of apnea. *Sleep* 1995;18:158-66
42. Kales A, Cadieux RJ, Bixler EO et al. Severe obstructive sleep apnea. I: Onset clinical course, and characteristics. *J Chron Dis* 1985;38:419-25
43. Hajduk IA, Strollo PJJ, Jasani RR, et al. Prevalance and predictor of nocturia in obstructive sleep apnea-hypopne syndrome-a retrospective study. *Sleep* 2003; 26: 61-4
44. Wise SK, Wise JC, DelGaudio JM. Gastroesophageal reflux and laryngopharyngeal reflux in patient with sleep- desordered breathing. *Otolaryngol Head Neck Surg* 2006;135:253-57
45. Strohl KP , Brown DB , Collop N , et al. ATS Ad Hoc Committee on Sleep Apnea, Sleepiness, and Driving Risk in Noncommercial Drivers. An official American Thoracic Society Clinical Practice Guideline: sleep apnea, sleepiness, and driving risk in noncommercial drivers. An update of a 1994 statement. *Am J Respir Crit Care Med.* 2013;187:1259-66
46. Findley L, Unverzadt M, Suratt P et al: Automobile accidents in patient with obstructive sleep apnea. *Am Review Res. Dis.* 140: 529-530; 1998
47. McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med* 2016;375:919-31.
48. Rundo JV. Obstructive sleep apnea basics. *Cleveland Clinic Journal of Medicine.* vol.86,supp.1, september 2019.

49. Marais J: The value of sleep nasendoscopy : a comparison between snoring and non-snoring patients. *Clin. Otolaryngol.* 23: 74-76, 1998
50. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med* 2017; 13(3):479–504
51. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med.* 2001;163:19–25
52. Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea–hypopnea and incident stroke. *Am J Respir Crit Care Med* 2010;182:269-77
53. Spence DL, Allen RC, Lutgendorf MA, et al. Association of obstructive sleep apnea with adverse pregnancy-related outcomes in military hospitals. *Eur J Obstet Gynecol Reprod Biol* 2017;210:166-72
54. Guilleminault C, Palombini L, Poyares D, et al. Pre-eclampsia and nasal CPAP:part 1. Early intervention with nasal CPAP in pregnant women with risk-factorsfor pre-eclampsia: preliminary findings. *Sleep Med* 2007;9:9-14
55. Poyares D, Guilleminault C, Hachul H, et al. Pre-eclampsia and nasal CPAP:part 2. Hypertension during pregnancy, chronic snoring, and early nasal CPAP intervention. *Sleep Med* 2007;9:15-21
56. Kaw R, Chung F, Pasupuleti V, et al. Meta-analysis of the association between obstructive sleep apnoea and postoperative outcome. *Br J Anaesth* 2012;109:897-906
57. Patil SP,Ayappa IA, Caples SM, et al. Treatment of adult obstructive sleep apnea with positive airway pressure: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med.* 2019;15:335-43
58. Adachi Y. Behavior therapy for obesity. *Japon Medical Association Journal* 2005; 48(11):539-44
59. Latner JD, Wilson GT, Stunkard AJ, Jackson ML. Self-help and long-term behavior therapy for obesity. *Behav Res Ther* 2002;40(7):805-12
60. Ogden CL, Carrol MD, Curtin LR, et al. Prevalance of overweight and obesity in United States, 1999-2004. *JAMA* 2006; 295:1549-55
61. Schwartz AR. Gold AR, Schubert N. at al. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis* 1991;144:494-98
62. Strobel RJ, Rosen RC.Obesity and weight loss in obstructive sleep apnea: a critical review. *Sleep* 1996;19:104-15
63. Tuomilehto HPI, Seppä JM, Partinen MM, et al; Kuopio Sleep Apnea Group. Lifestyle intervention with weight reduction: first-line treatment in mild obstructive sleep apnea. *Am J Respir Crit Care Med* 2009; 179(4):320–327
64. Fritsher LG, Mottin CC, Canani S, Chatkin JM. Obesity obstructive sleep apnea-hypopnea syndrome: the impact of bariatric surgery. *Obes Surg.* 2007;17(1):95-99
65. Ip MS, Lam KS, Ho C, Tsang KW, Lam W.Serum leptin and vascular risk factors obstructive sleep apnea. *Chest* 2000;118(3):580-86
66. Sarkhosh K, Switzer NJ, El-Hadi M, Birch DW, Shi X, Karmali S. The impact of bariatric surgery on obstructive sleep apnea: a systematic review. *Obes Surg* 2013; 23(3):414–423
67. Lettieri CJ, Eliasson AH, Greenburg DL. Persistence of obstructive sleep apnea after surgical weight loss. *J Clin Sleep Med.*2008;4(4):333-338
68. Greenburg DL, Lettieri CJ, Eliasson AH. Effects of surgical weight loss on measures of obstructive sleep apnea: a meta-analysis.*Am J Med.*2009;122(6):535-542

69. Strohl KP, Redline S. Recognition of obstructive sleep apnea. *Am J Crit Care Med* 2005; 165:2408-13
70. Gonnissen H.K.J., Hulshof ve M.S. Westerterp-Plantenga, "Chronobiology, Endocrinology, and Energy-and-Food-Reward Homeostasis" *Obesity Reviews* 14 no.5(May 2013): 405-416, doi: 10.1111/obr12019
71. Caples SM, Rowley JA, Prinsell JR, et al. Surgical modifications of the upper airway for obstructive sleep apnea in adults: a systematic review and meta-analysis. *Sleep* 2010; 33(10):1396–1407
72. Aurora RN, Casey KR, Kristo D, et al. Practice parameters for the surgical modifications of the upper airway for obstructive sleep apnea in adults. *Sleep* 2010; 33(10):1408–1413
73. Mickelson SA : Upper airway bypass surgery for obstructive sleep apnea syndrome. *Otolaryngol Clin N Am.* 31(6) 1013-23; 1998
74. Köktürk O. Uykuda solunum bozukluğu sınıflaması, tanımlar ve obstrüktif uyku apne sendromu. *Epidemiyoloji ve klinik bulgular. Türkiye Klinikleri J Pulm Med-Special Topics* 2008; 1: 40-5
75. Zafar S, Ayappa I, Norman RG et al. Choise of oximeter effects apnea-hypopnea index. *Chest* 2005;127(1): 80-88
76. Chowdhuri S , Quan SF , Almeida F , et al. ATS Ad Hoc Committee on Mild Obstructive Sleep Apnea. An official American Thoracic Society research statement: impact of mild obstructive sleep apnea in adults. *Am J Respir Crit Care Med.* 2016;193:e37-54
77. Jin F, Liu J, Zhang X, Cai W, Zhang Y, Zhang W, Yang J, Lu G, Zhang X. Effect of continuous positive airway pressure therapy on inflammatory cytokines and atherosclerosis in patients with obstructive sleep apnea syndrome. *Mol Med Rep.* 2017;16(5): 6334–6339
78. Engleman HM, Wild MR. Improving CPAP use by patients with the sleep apnoea/hypopnoea syndrome (SAHS). *Sleep Med Rev* 2003;7:81-99
79. Teschler H, Berthon-Jones M, Wessendorf T, et al. Influence of moderate alcohol consumption on obstructive sleep apnoea with and without AutoSet nasal CPAP therapy. *Eur Respir J* 1996;9:2371-7
80. Mazzotti DR ,Keenan BT, Lim DC, et al.Symptom subtypes of obstructive sleep apnea predict incidence of cardiovascular outcomes.*Am J Respir Crit Care Med.*2019;200:493-506
81. Öztürk L, Kaynak H. Nazal CPAP tedavisi. "Obstrüktif uyku apnesi sendromu ve horlama"da(Editör Ömür M, Elez F) İstanbul 2002, Sayfa 81-85
82. Kushida C, Morgenthaler T, Littner M. Practice parameters fort he treatment of snoring and obstructive sleep apnea with oral appliances: an update for 2005.*Sleep* 2006;29(2):240-43
83. Ramar K, Dort LC, Katz SG, et al. Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015—an American Academy of Sleep Medicine and American Academy of Dental Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med* 2015; 11(7):773–827
84. Millman RP, Rosenberg CR, Kramer NR: Oral appliances in the traetment of sleep apnea.*Otolarngol Clin N Am.*31(6):1039-1048;1998
85. Schmidt-Nowara WW, Meade TE, Hays MB: Treatment of snoring and obstructive sleep apnea with dental orthosis. *Chest* 99:1378-1385;1991

86. Bachour P, Bachour A, Kauppi P, et al. Oral appliance in sleep apnea treatment: respiratory and clinical effects and long-term adherence. *Sleep Breath* 2016;20:805-12
87. Gagnadoux F, Pepin JL, Vielle B, et al. impact of mandibular advancement therapy on endothelial function in severe obstructive sleep apnea. *Am J Respir Crit Care Med* 2017;195:1244-52
88. Srijithesh PR, Aghoram R, Goel A, et al. Positional therapy for obstructive sleep apnoea. *Cochrane Database Syst Rev.* 2019;5:CD010990
89. Randerath WJ, Verbraecken J, Andreas S, et al. Non-CPAP therapies in obstructive sleep apnoea. *Eur Respir J* 2011;37:1000-28
90. Chan AS, Lee RW, Cistulli PA. Non-positive airway pressure modalities: mandibular advancement devices/positional therapy. *Proc Am Thorac Soc* 2008;5:179-84
91. Woodson BT, Soose RJ, Gillespie MB, STAR Trial Investigators. Three-year outcomes of cranial nerve stimulation for obstructive sleep apnea: the STAR Trial. *Otolaryngol Head Neck Surg* 2016; 154(1):181-188
92. Kent DT, Lee JJ, Strollo PJ Jr., Soose RJ. Upper airway stimulation for OSA: early adherence and outcome results of one center. *Otolaryngol Head Neck Surg* 2016; 155(1):188-193
93. Shah J, Russell JO, Waters T, Kominsky AH, Trask D. Uvulopalato-pharyngoplasty vs CN XII stimulation for treatment of obstructive sleep apnea: a single institution experience. *Am J Otolaryngol* 2018; 39(3):266-270
94. Huntley C, Kaffenberger T, Doghramji K, Soose R, Boon M. Upper airway stimulation for treatment of obstructive sleep apnea: an evaluation and comparison of outcomes at two academic centers. *J Clin Sleep Med* 2017; 13(9):1075-1079
95. Berry RB, Kryger MH, Massie CA. A novel nasal expiratory positive airway pressure (EPAP) device for the treatment of obstructive sleep apnea: a randomized controlled trial. *Sleep* 2011; 34(4):479-485
96. Kryger MH, Berry RB, Massie CA. Long-term use of a nasal expiratory positive airway pressure (EPAP) device as a treatment for obstructive sleep apnea (OSA). *J Clin Sleep Med* 2011; 7(5):449-453
97. Freire AO, Sugai GC M, Chrispin FS, et al. Treatment of moderate obstructive sleep apnea syndrome with acupuncture: a randomised, placebo-controlled pilot trial. *Sleep Medicine.* 2007;8(1):43-50
98. Lv Z. T., Jiang W. X., Huang J. M., Zhang J. M., Chen A. M. The clinical effect of acupuncture in the treatment of obstructive sleep apnea: a systematic review and meta-analysis of randomized controlled trials. *Evidence-Based Complementary and Alternative Medicine.* Vol.2016; 10 pages.2016
99. Wang L, Xu J, Zhan Y, Pei J. Acupuncture for Obstructive Sleep Apnea (OSA) in Adults: A Systematic Review and Meta-Analysis. *Biomed Res Int.* Vol.2020 Mar 5;2020: 10 pages
100. Croft CB, Pringle MB. Snoring abn sleep apnoea. *Scott-Brown Otolaryngology*(6. Baskı) Volüm 4;19. Bölüm. Butterword-Heinemann Oxford. 1997
101. Jokick R, Klimaszevski A, Mink J, Fitzpatrick MF: Surface tension forces in the sleep apnea: the role of soft tissue lubricant: a randomized double-blind placebo controlled trial. *Am J Resp Crit Care Med.* 157:1522-25;1998
102. Sara Elisa M Mattar et al. Skeletal and Occlusal Characteristics in Mouth-Breathing Pre-School Children. *J Clin Pediatr Dent.* Summer 2004
103. American Thoracic Society. Standards and indication for cardiopulmonary sleep studies in children. *Am J Respir Crit Care Med* 1996;153:866-78

104. Montgomery-Downs HE, Crabtree VM, Gozal D. Cognition, sleep and respiration in at-risk children treated for obstructive sleep apnoea. *Eur Respir J* 2005; 25:336-42
105. Benninger M, Walner D. Obstructive sleep-disordered breathing in children. *Clin Cornerstone* 2007;9:6-12
106. Redline S, Storfer-Isser A, Rosen CL, et al. Association between metabolic syndrome and sleep-disordered breathing in adolescents. *Am J Respir Crit Care Med* .2007 ; 176 (4):401 – 408
107. Nixon GM, Brouillette RT. Diagnostic techniques for obstructive sleep apnoea: is polysomnography necessary? *Paediatr Respir Rev* 2002;3:18-24
108. Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, et al. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study. *Am J Respir Crit Care Med* 2010;182:676-83
109. Resta O, Foschino-Barbaro MP, Legari G, et al. Sleep-related breathing disorders, loud snoring and excessive daytime sleepiness in obese subjects. *Int J Obes Relat Metab Disord*.2001;25(5):669-675
110. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep disordered breathing. *JAMA*.2000;284(23):3015-3021
111. Vgontzasa AN, Bixler EO, Chrousos GP. Sleep apnea is a manifestation of the metabolic syndrome. *Sleep Medicine Review*(2005)9:211-224
112. Phillips BG, Hisel TM, Kato M, et al. Recent weight gain in patients with newly diagnosed obstructive sleep apnea. *J Hypertens*. 1999;17(9):1297-1300
113. Chin K, Shimizu K, Nakamura T, et al. Changes in intraabdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. *Circulation*.1999;100(7):706-712
114. Popko K, Gorska E, Wasik M, et al. Frequency of distribution of leptin gene polymorphism in obstructive sleep apnea patients. *J Physiol Pharmacol* .2007 ; 58 (Suppl 5) (Pt. 2): 551 – 561
115. Rowley JA, Williams BC, Smith PL, Schwartz AR. Neuromuscular activity and upper airway collapsibility: mechanisms of action in the decerebrate cat. *Am J Respir Crit Care Med* 1997;156:515–521
116. Fogel RB, Malhotra A, Pillar G. et al. Increased prevalence of obstructive sleep apnea syndrome in obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2001;86:1175-80
117. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnea is independently associated with insulin resistance. *Am J Respir Crit Care Med* .2002 ; 165 (5):670 – 676
118. Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE; Sleep Heart Health Study Investigators. Sleep disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. *Am J Epidemiol*.2004;160(6):521–530
119. Li J, Thorne LN, Punjabi NM, et al. Intermittent hypoxia induces hyperlipidemia in lean mice. *Circ Res* . 2005;97(7):698-706
120. Ishida K, Kato M, Kato Y, et al. Appropriate use of nasal continuous positive airway pressure decreases elevated C-reactive protein in patients with obstructive sleep apnea. *Chest*.2009;136(1):125-129
121. de Lima FF, Mazzotti DR, Tufik S, Bittencourt L. The role inflammatory response genes in obstructive sleep apnea syndrome: a review. *Sleep Breath*. 2016;20(1):331–338

122. Ceccato F, Bernkopf E, Scaroni C. Sleep apnea syndrome in endocrine clinics. *J Endocrinol Invest.* 2015;38(8):827–834
123. Spiegel K , et al. Leptin levels are dependent on sleep duration: relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. *J Clin Endocrinol Metab.* 2004;89(11):5762-5771
124. Polotsky VY , Smaldone MC , Scharf MT , et al . Impact of interrupted leptin pathways on ventilatory control. *J Appl Physiol.* 2004;96(3):991-998
125. Phillips BG , Kato M , Narkiewicz K , Choe I , Somers VK .Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea. *Am J Physiol Heart Circ Physiol.* 2000;279(1):H234-H237
126. Zhang XL, Yin KS, Li C, Jia EZ, Li YQ, Gao ZF. Effect of continuous positive airway pressure treatment on serum adiponectin level and mean arterial pressure in male patients with obstructive sleep apnea syndrome . *Chin Med J (Engl).* 2007;120(17):1477-1481
127. Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med.* 2004;141(11):846-850
128. Li M, Li X, Lu Y. Obstructive Sleep Apnea Syndrome and Metabolic Diseases. *Endocrinology.* 2018 Jul 1;159(7):2670-2675
129. Spiegel K, Knutson K, Leproult R, et al. Sleep loss: A novel risk factor for insulin resistance and type 2 diabetes. *J Appl Physiol* 2005;99:2008–2019
130. Al-Delaimy WK, Manson JE, Willett WC, Stampfer MJ, Hu FB. Snoring as a risk factor for type II diabetes mellitus: a prospective study. *Am J Epidemiol* 2002;155:387–93./// Elmasry A, Janson C, Lindberg E, Gislason T, Tageldin MA, Boman G. The role of habitual snoring and obesity in the development of diabetes: a 10-year follow-up study in a male population. *J Int Med* 2000;248:13–20
131. Dixon JB, Schachter LM, O’Brien PE. Polysomnography before and after weight loss in obese patients with severe sleep apnea. *Int J Obes (Lond).* 2005;29(9):1048-1054
132. Meerlo P, A. Sgoifo, and D. Suchecki, “ Restrictide and Disrupted Sleep: Effect on Autonomic Function, Neuroendocrine Stress Systems and Stress Responsivity” *Sleep Medicine Reviews* 12, no.3 (June 2008):197-210
133. Walker MP. “Sleep and Memory and Emotion” *Progress in Brain Research* 185(2010):49-68
134. Phillips CL, Grunstein RR, Darendeliler MA, et al. Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med.* 2013;187:879-87
135. White DP, Shafazand S. Mandibular advancement device vs. CPAP in treatment of obstructive sleep apnea: are they equally effective in short term health outcomes?. *J Clin Sleep Med.* 2013;9:971-2.
136. Tan YK, L’Estrange PR, Luo YM, Smith C, Grant HR, Simonds AK, et al. Mandibular advanced splint and continuous positive airway pressure in patients with obstructive sleep apnoea: a randomized cross-over trial. *Eur J Ortod.* 2002;24:239-49.
137. Bolling SM. Encouraging CPAP adherence: its everyone’s jobs. *Respir Care.* 2010;55:1230-9
138. Budhiraja R et al. Early CPAP use identifies subsequent adherence to CPAP therapy. *Sleep.* 2007;30.320-4

139. Lettieri CJ, Shah AA, Holey AB, Kelly WF, Chang AS, Roop SA, et al. Effects of a short course of eszopiclone on continuous positive airway pressure adherence: a randomized trial. *Ann Intern Med.*2009;151:696-702
140. Wiman Eriksson E, Leissner L, Isaacsson G, Fransson A. A prospective 10-year follow-up polygraphic study of patients treated with a mandibular protruding device. *Sleep Breath.* 2014;19:393-401
141. de Almeida FR, Lowe AA, Tsuiki S, Otsuka R, Wong M, Fastlicht S, et al. Long-term compliance and side effects of oral appliances used for treatment of snoring and obstructive sleep apnea syndrome. *J Clin Sleep Med.* 2015;15:143-52
142. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet.*2014;383:736-47
143. Clark GT, Sohn JW, Hong CN. Treating obstructive sleep apnea and snoring: Assessment of an anterior mandibular positioning device. *J Am Dent Assoc* 2000;131:765-71
144. Ünlü M, İriz A, Doğan BA. et al. Relationship Between Obesity with Symptoms and Findings of Obstructive Sleep Apnea Syndrome. *J Med Updates* 2014;4(1):11-15.