Published in final edited form as:

Clin Geriatr Med. 2015 February ; 31(1): 139–ix. doi:10.1016/j.cger.2014.08.023.

Obstructive Sleep Apnea and Type 2 Diabetes in Older Adults

Karoline Moon, MD, Naresh M. Punjabi, MD, PhD, and Rashmi N. Aurora, MD

Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, School of Medicine

SYNOPSIS

In older adults, obstructive sleep apnea (OSA) and type 2 diabetes mellitus are prevalent medical conditions each with adverse clinical consequences. Over the last decade, there has been increased recognition that OSA is highly prevalent in people with type 2 diabetes and that metabolic conditions such as insulin resistance, glucose intolerance, and type 2 diabetes are common in people with OSA. Intermittent hypoxemia and recurrent arousals in OSA trigger a repertoire of pathophysiological events including activation of the sympathetic nervous system, increase in oxidative stress, alterations in corticotropin function, and release of inflammatory adipocytokines. These pathophysiological alterations can alter normal glucose homeostasis and may increase the risk for type 2 diabetes. Conversely, there is also evidence that type 2 diabetes may alter OSA progression and promote the expression of central sleep apnea. Cheyne-Stokes or periodic breathing and central disordered breathing events during sleep are more common in people with type 2 diabetes. It has been suggested that diabetes-associated autonomic dysfunction could possibly result in instability of respiratory control via enhanced central chemoreceptor-mediated gain as well as cardiac impairments with prolonged circulatory time. While more research is needed to clarify the mechanisms underlying the bi-directional association between OSA and type 2 diabetes, the frequent co-existence of these two conditions should prompt all health care professionals to embrace clinical practices that include screening a patient presenting with one disorder for the other particularly in older adults.

Keywords

Obstructive sleep apnea; central sleep apnea; type 2 diabetes; aging

INTRODUCTION

Given the global increase in prevalence of obesity, obstructive sleep apnea (OSA) is becoming an increasingly common and pervasive condition. It has been estimated that OSA affects 12–18 million people in the United States alone¹. In addition to its well-established neurocognitive effects², OSA has also been found to be an independent risk factor for

Corresponding Author: Rashmi N. Aurora, MD, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, 5501 Hopkins Bayview Circle, Baltimore, MD 21224, Phone: (410) 550-0574, Fax: (410) 550-2612, rashmi.n.aurora@gmail.com.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

hypertension³, cardiovascular disease⁴, and impaired glucose metabolism⁵. Cross-sectional studies of clinic and population-based samples suggest that up to 50% of patients with OSA have type 2 diabetes and approximately 50% of patients with type 2 diabetes have moderate to severe OSA^{6; 7}. While many of the putative links between OSA and metabolic dysfunction are not well elucidated, it is likely that intermittent hypoxemia and sleep fragmentation, the two pathophysiological concomitants of OSA, play a fundamental role in the development of insulin resistance, glucose intolerance, and type 2 diabetes. The central theme of this review is to provide a brief appraisal of the bidirectional nature of the association between OSA and type 2 diabetes given that both conditions are increasingly prevalent in older adults.

Sleep Apnea: Disease Definition and Risk Factors

Sleep apnea is a group of chronic sleep-related breathing disorders that are characterized by the occurrence of disordered breathing events during sleep. These events are generally classified into two main types: obstructive and central. The classification of an event as obstructive or central is dependent on whether, in the absence of airflow, there is ongoing respiratory effort. OSA, which is the most prevalent type of sleep apnea, is characterized by the predominance of recurrent obstructive events that result from partial or complete collapse of the upper airway during sleep. The ensuing cessation of airflow (apneas) or decrease in airflow (hypopneas) is associated with a decrease in oxyhemoglobin saturation and arousal from sleep. In OSA, apneas and hypopneas during sleep are associated with continued respiratory effort. In contrast, in central sleep apnea, the upper airway remains patent and the apneas and hypopneas result during sleep from a decrease or lack of respiratory muscle effort. The apnea-hypopnea index (AHI), which is the number of apneas and hypopneas per hour of sleep, is used as the disease-defining metric for obstructive and central sleep apnea. By convention, the following thresholds are used to classify the severity of obstructive or central sleep apnea: normal (AHI < 5 event/hr), mild (AHI: 5.0–14.9 events/hr), moderate (AHI: 15.0–29.9 events/hr), or severe (AHI > 30 events/hr). Although OSA is by far the more common type, obstructive and central sleep apnea can coexist in older adults. Data from several large population-based cohort studies have estimated the prevalence of OSA to vary in the range of 5.0% to 15.0%⁸. Even more gripping, is the large number of people with OSA who remain undiagnosed – estimated to be 70–90% of those with OSA⁹. Risk factors for OSA include advancing age, male sex, family history, excess body fat, central obesity, large neck circumference, as well as craniofacial and upper airway abnormalities⁸. Other risk factors include family history, smoking, being post-menopausal, and nighttime alcohol use.

Age as a Risk Factor for Sleep Apnea

Even in the absence of an underlying sleep disorder, older age is associated with impairments in sleep quality that can be related to either chronic medical or psychiatric conditions and/or changes in social situation¹⁰. The presence of a sleep disorder such as OSA can further impair sleep quality. Studies investigating prevalence of OSA have generally shown that it is age-related condition with older adults having a higher prevalence compared to younger adults^{11–15}. Point estimates of OSA prevalence, however, vary across

studies, in part, because of the heterogeneity in study samples including recruitment source (clinic versus community-based), distribution of factors such as sex and body weight, and the methods used to identify OSA. Undoubtedly, the highest prevalence of OSA is in older men with estimates in the range of 13% to 44% for those that are 59–99 years old^{11–15}. Cross-sectional data on OSA prevalence as a function of age suggest that prevalence increases in middle-aged adults, up to the sixth decade of life, with a subsequent plateau (Figure 1)¹⁶. Longitudinal data on older cohorts also indicate a plateau, or perhaps even a decline, in OSA prevalence in the elderly^{17; 18}. It is certainly possible that survivor bias could explain the lack of a monotonic increase in OSA prevalence with age because the high prevalence of age-related comorbid conditions (e.g., stroke, heart failure) may preclude participation of older adults in clinic and epidemiological studies.

Risk factor profiles for OSA seem to vary as a function of increasing age. For example, body mass index (BMI) does not demonstrate the same strength of association in elderly as it does in young or middle-aged adults^{16; 19–22}. In fact, in the elderly, a declining trajectory of BMI has been associated with increasing OSA severity as assessed by the AHI²². A decrease in BMI, which may reflect loss of muscle mass, could be associated with decrease in functional activity of upper airway dilator muscles (e.g., genioglossus) in the elderly²³. Alterations in upper airway mechanics and anatomy (e.g., increased pharyngeal fat pads or changes in bony structure) with aging can increase upper airway collapsibility and predispose to the occurrence of obstructive apneas and hypopneas during sleep^{23; 24}. Moreover, the higher prevalence of other chronic medical conditions such as congestive heart failure and stroke and the use of centrally acting medications (e.g., opioids for chronic pain) can further escalate the risk for central sleep apnea and augment the untoward associated effects of intermittent hypoxemia and sleep disruption on health-related consequences. Thus, while BMI, central obesity, and sex have a substantial role in mediating OSA risk in younger and middle-aged adults, other factors have a greater influence on the development of obstructive or central sleep apnea in older adults. It is also important to recognize that the clinical manifestations and presentation of OSA can be distinct between older and younger or middle-aged adults. Reports of snoring, witnessed apneas, and other presenting symptoms for OSA are less common in older people than their younger counterparts^{16; 25}. Such differences underscore the importance of heightened vigilance in evaluating the older patients if they report poor sleep quality or daytime sleepiness. In the sections that follow, the epidemiology of metabolic abnormalities is briefly reviewed followed by an appraisal of the evidence on the bidirectional association between OSA and type 2 diabetes.

Disorders of Glucose of Metabolism: Definition and Epidemiology

Four distinct categories of diabetes mellitus have been proposed by the American Diabetes Association²⁶. Type 1 diabetes, which account of 5–10% of all diabetes cases, develops as a result of pancreatic beta-cell destruction and associated impaired insulin secretion. In contrast, type 2 diabetes, which accounts for accounts 90–95% of all diabetes cases, is characterized by insulin resistance coupled with impairments in insulin secretion. Gestational diabetes is the third category of diabetes which is diagnosed in the presence of any degree of glucose intolerance with onset of pregnancy and complicates about 4% of all pregnancies in the U.S. Finally, the fourth category of diabetes includes genetic β -cell

defects or defects in insulin action, pancreatic disease, endocrinopathies, drug-induced, infection and genetic syndromes. The criteria for the diagnosis of diabetes require any one of the following: (a) fasting blood glucose ≥ 126 mg/dl; (b) a random blood glucose ≥ 200 mg/dl and symptoms of hyperglycemia (i.e., polyuria, polydipsia and unexplained weight loss); or (c) two-hour blood glucose ≥ 200 mg/dl during an oral glucose tolerance test. In addition to the four categories of diabetes described above, there are two clinically relevant pre-diabetic conditions which include impaired fasting glucose and impaired glucose tolerance. Impaired fasting glucose is defined as a fasting blood glucose level between 100 mg/dl and 126 mg/dl. Impaired glucose tolerance is defined as a 2-hour blood glucose level between 140 mg/dl and 200 mg/dl during an oral glucose tolerance test.

Along with obesity, diabetes mellitus has also become a global epidemic and affects approximately 7.7% of the world's population with more than 90% of the cases being type 2 diabetics²⁷. Prevalence estimates for type 2 diabetes range from 0.3 to 17.9% in Africa, 1.2 to 14.6% in Asia, 0.7 to 11.6% in Europe, 4.6 to 40.0% in the Middle East, 6.7 to 28.2% in North America and 2.0 to 17.4% in South America²⁸. The development of type 2 diabetes is a complex, multi-step process that is influenced by both genetic and environmental factors. Without doubt, genetic susceptibility plays a significant role in the etiology of type 2 diabetes as supported by studies of monozygotic twin which show a concordance of nearly 100%²⁹. Increased body fat, visceral adiposity, and sedentary life style are some of other well-known risk factors for type 2 diabetes. Moreover, the increasing prevalence of diabetes over the past two decades has been predominantly in people that are 65 years in age or older³⁰. In fact, 40% of people in the US and more than 50% of people worldwide with type 2 diabetes are over the age of 65 years. Furthermore, it is estimated that by the year 2050 there will be at least a 4.5-fold increase in the number of people over 65 years in age with type 2 diabetes³⁰. The higher predisposition for developing type 2 diabetes with increasing age is due to the age-related decrease in whole-body insulin sensitivity and insulin secretion from the pancreatic beta-cell. The decline in insulin insensitivity with age is attributable to muscle fat accumulation and a reduction in mitochondrial function in muscle³¹. Over the last two decades, there has been increased recognition the OSA may also predispose to the development of type 2 diabetes which, in turn, may over time worsen OSA severity and establish a potentially feed forward loop as described below.

Obstructive Sleep Apnea as a Cause of Metabolic Dysfunction and Type 2 Diabetes

The association between OSA and metabolic abnormalities such as insulin resistance and type 2 diabetes has been generally characterized using several lines of parallel inquiry^{32; 33}. These have included (a) correlating metabolic abnormalities to either OSA-related symptoms or OSA severity as assessed by nocturnal recordings of sleep and breathing; and (b) assessing whether OSA treatment with positive airway pressure (PAP) therapy has any favorable effects on measure glucose metabolism or glycemic control. Studies on the association between OSA-related symptoms (e.g., snoring, witnessed apneas) and glucose metabolism have consistently demonstrated an independent association between OSA and abnormalities such as impaired fasting glucose, glucose intolerance, and type 2

diabetes^{32; 33}. Consistently, patients with OSA have been shown to have a higher prevalence of type 2 diabetes and metabolic syndrome even after accounting for confounding covariates such as age and BMI. However, the use of surrogate measures to assess OSA (e.g., snoring, witnessed apneas) in these studies represents a major weakness as it provides little insight into the biological mechanisms responsible for the observed association. Fortunately, studies that have used polysomnography to characterize breathing abnormalities during sleep have by and large found an independent association between OSA and metabolic dysfunction^{32; 33}. OSA severity, as assessed by the AHI and severity of nocturnal oxyhemoglobin desaturation, has been associated with a repertoire of metabolic parameters including higher fasting insulin and glucose levels, a high prevalence of an abnormal oral glucose tolerance test, and impaired insulin sensitivity as assessed by hyperinsulinemic euglycemic clamp^{32; 33}. Moreover, consideration for confounding factors such as age, BMI, and waist circumference in many of the published studies has provided credence to the hypothesis that OSA is independently, and perhaps causally, associated with metabolic abnormalities including type 2 diabetes.

Given the collective weight of cross-sectional and some longitudinal data linking OSA to insulin resistance, glucose tolerance and type 2 diabetes, it is surprising that studies on OSA treatment have failed to demonstrate consistent improvements in metabolic function or glycemic control^{32; 33}. However, much of the available evidence on treatment is based on uncontrolled studies that suffer from a number of methodological flaws including poor adherence to PAP therapy, limited duration of therapy, and small sample size. Thus, definitive conclusions regarding the metabolic implications of OSA therapy with PAP require additional research. Even if well-controlled larger randomized clinical trials in the future demonstrate that PAP therapy does not improve glycemic control, it does not refute the possibility that OSA can induce metabolic abnormalities that can eventually lead to type 2 diabetes. Indeed, a number of animal and human studies have shown that intermittent hypoxia and sleep fragmentation can initiate a repertoire of pathophysiological effects that can alter normal glucose homeostasis. Exposure to conditions of sustained or intermittent hypoxia can decrease insulin sensitivity and impair insulin secretion – defects that are fundamental to the pathogenesis of type 2 diabetes. Thus, OSA is likely to be of relevance in the older adult who is likely to have a higher predisposition for OSA and for metabolic dysfunction. Moreover, OSA-related disruption of sleep continuity may also adversely affect glucose metabolism. Although empirical data on the effects of sleep fragmentation are limited, two independent groups have demonstrated negative effects of sleep fragmentation on insulin sensitivity in normal subjects^{34; 35}. The mechanisms through which intermittent hypoxemia and sleep fragmentation could affect glucose metabolism are summarized in Figure 2 and include: (a) alterations in sympathetic nervous system activity; (b) changes in activity of hypothalamic-pituitary-adrenal (HPA) axis; (c) formation of reactive oxygen species; and (d) increases in inflammatory cytokines (i.e., interleukin-6 and tumor necrosis factor- α and adipocyte derived factors (i.e., leptin, adiponectin, and resistin)³⁶.

Type 2 Diabetes as a Risk Factor for OSA

While much of the foregoing discussion has focused on OSA as a risk factor for metabolic conditions, the possibility of reverse causation (i.e., metabolic conditions such as type 2

diabetes leading to OSA) needs to be also considered (Figure 2). Indeed, a number of clinic-based studies have shown that patients with type 2 diabetes are more likely to have obstructive and central sleep apnea^{37–42}. A remarkable feature across these studies is the observation that coexisting autonomic neuropathy substantially increases the prevalence of obstructive and central sleep apnea in these patients. Nonetheless, numerous methodological limitations in the available studies prohibit inferences regarding cause and effect and greatly limit the generalizability of the available data. Such issues notwithstanding, investigators from the Sleep Heart Health Study⁶ have shown that even after adjusting for confounders such as obesity and prevalent cardiovascular disease, middle-aged and older adults with longstanding type 2 diabetes in the general community are more likely to show evidence of periodic breathing during sleep. Surprisingly, no differences were observed between diabetic and nondiabetic subjects in the frequency obstructive events. Mechanisms underlying the higher prevalence of central sleep apnea in people with type 2 diabetes are not well understood. Animal models with chemically induced diabetes suggest that abnormal ventilatory responses to hypoxia and/or hypercapnia may be partially responsible. Studies in diabetic patients also show that abnormalities in O₂ and CO₂ sensitivity may have an important role in increasing respiratory control instability during sleep^{43; 44}. Whether diabetes also contributes to mechanical alterations in the upper airway and thus increasing upper airway collapsibility during sleep remains an open question.

Interactions of Age, Sleep Apnea, and Type 2 Diabetes

It is also possible that age itself may interact with OSA and augment the predisposition for type 2 diabetes (Figure 3). While the exact mechanisms for the age-related susceptibility to type 2 diabetes are not known, glucose-stimulated insulin sensitivity and insulin secretion decline with age and result in fasting and postprandial hyperglycemia⁴⁵. In older adults, OSA may accelerate the age-related progression to glucose intolerance and eventually to type 2 diabetes because of the OSA-induced increase in sympathetic nervous system activation and oxidative stress which, in turn, can decrease peripheral insulin sensitivity and secretion. Conversely, it is also possible that type 2 diabetes may augment the known effects of age-related risk of OSA. Decreases in muscle function and muscle with older age may be hastened in the presence of type 2 diabetes. Insulin resistance and dysglycemia, or both, are known risk factors for accelerated muscle loss that results because of decreased stimulation of protein synthesis pathways and increased activation of protein degradation pathways³¹. Thus, age and type 2 diabetes may heighten each other's impact on upper airway function and amplify the risk of OSA. Whether these interactions between age, sleep apnea, and type 2 diabetes exist and whether they are either additive or multiplicative remains to be determined. Such limitations notwithstanding, there is little doubt that the past decade has seen major advances in our understanding of the associations between sleep apnea, glucose intolerance, insulin resistance, and type 2 diabetes. Despite the remarkable advancements, the enthusiasm to implicate causal bidirectional links between OSA and type 2 diabetes has to be somewhat tempered by the fact that both conditions share common risk factors such as obesity. Thus, the challenge that lies ahead is to need to collect additional evidence that will support the hypothesis of a causal association and help define whether age modifies these associations particularly given that both conditions are common in older

adults. A multi-disciplinary effort with expertise from various specialties in medicine will provide the foundation on which the complex tapestry that connects age, sleep apnea, and type 2 diabetes can be unwound. Fortunately, the interest in the overlap of these conditions is in its infancy and a substantial work lies ahead to enhance our ability to answer fundamental questions regarding the bidirectional association between OSA and type 2 diabetes.

Acknowledgments

Dr. Punjabi was supported by National Institutes of Grant (HL075078). Dr. Aurora was supported by a grant by the American Sleep Medicine Foundation.

REFERENCES

1. U.S. Department of Health and Human Services. Wake up America: A National Sleep Alert. Bethesda, MD: 1993.
2. Vaessen TJ, Overeem S, Sitskoorn MM. Cognitive complaints in obstructive sleep apnea. *Sleep Med Rev.* 2014
3. Konecny T, Kara T, Somers VK. Obstructive sleep apnea and hypertension: an update. *Hypertension.* 2014; 63(2):203–209. [PubMed: 24379177]
4. Kasai T, Floras JS, Bradley TD. Sleep apnea and cardiovascular disease: a bidirectional relationship. *Circulation.* 2012; 126(12):1495–1510. [PubMed: 22988046]
5. Iftikhar IH, Khan MF, Das A, et al. Meta-analysis: continuous positive airway pressure improves insulin resistance in patients with sleep apnea without diabetes. *Ann Am Thorac Soc.* 2013; 10(2): 115–120. [PubMed: 23607839]
6. Resnick HE, Redline S, Shahar E, et al. Diabetes and sleep disturbances: findings from the Sleep Heart Health Study. *Diabetes Care.* 2003; 26(3):702–709. [PubMed: 12610025]
7. Foster GD, Sanders MH, Millman R, et al. Obstructive sleep apnea among obese patients with type 2 diabetes. *Diabetes Care.* 2009; 32(6):1017–1019. [PubMed: 19279303]
8. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc.* 2008; 5(2): 136–143. [PubMed: 18250205]
9. Young T, Evans L, Finn L, et al. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep.* 1997; 20(9):705–706. [PubMed: 9406321]
10. Ancoli-Israel S. Sleep and aging: prevalence of disturbed sleep and treatment considerations in older adults. *J Clin Psychiatry.* 2005; 66 Suppl 9:24–30. [PubMed: 16336039]
11. Ancoli-Israel S, Kripke DF, Klauber MR, et al. Sleep-disordered breathing in community-dwelling elderly. *Sleep.* 1991; 14(6):486–495. [PubMed: 1798880]
12. Ancoli-Israel S, Kripke DF, Klauber MR, et al. Natural history of sleep disordered breathing in community dwelling elderly. *Sleep.* 1993; 16(8 Suppl):S25–S29. [PubMed: 8178017]
13. Bixler EO, Vgontzas AN, Ten HT, et al. Effects of age on sleep apnea in men: I. Prevalence and severity. *Am J Respir Crit Care Med.* 1998; 157(1):144–148. [PubMed: 9445292]
14. Duran J, Esnaola S, Rubio R, et al. 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. [PubMed: 11254524]
15. Mehra R, Stone KL, Blackwell T, et al. Prevalence and correlates of sleep-disordered breathing in older men: osteoporotic fractures in men sleep study. *J Am Geriatr Soc.* 2007; 55(9):1356–1364. [PubMed: 17767677]
16. Young T, Shahar E, Nieto FJ, et al. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. *Arch Intern Med.* 2002; 162(8):893–900. [PubMed: 11966340]
17. Ancoli-Israel S, Gehrman P, Kripke DF, et al. Long-term follow-up of sleep disordered breathing in older adults. *Sleep Med.* 2001; 2(6):511–516. [PubMed: 14592266]

18. Sforza E, Gauthier M, Crawford-Achour E, et al. A 3-year longitudinal study of sleep disordered breathing in the elderly. *Eur Respir J*. 2012; 40(3):665–672. [PubMed: 22408210]
19. Newman AB, Nieto FJ, Guidry U, et al. Relation of sleep-disordered breathing to cardiovascular disease risk factors: the Sleep Heart Health Study. *Am J Epidemiol*. 2001; 154(1):50–59. [PubMed: 11434366]
20. Redline S, Kirchner HL, Quan SF, et al. The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. *Arch Intern Med*. 2004; 164(4):406–418. [PubMed: 14980992]
21. Bliwise DL. Epidemiology of age-dependence in sleep disordered breathing (SDB) in old age: The Bay Area sleep cohort (BASC). *Sleep Med Clin*. 2009; 4(1):57–64. [PubMed: 20161180]
22. Bliwise DL, Colrain IM, Swan GE, et al. Incident sleep disordered breathing in old age. *J Gerontol A Biol Sci Med Sci*. 2010; 65(9):997–1003. [PubMed: 20498222]
23. Eikermann M, Jordan AS, Chamberlin NL, et al. The influence of aging on pharyngeal collapsibility during sleep. *Chest*. 2007; 131(6):1702–1709. [PubMed: 17413053]
24. Strohl KP, Butler JP, Malhotra A. Mechanical properties of the upper airway. *Compr Physiol*. 2012; 2(3):1853–1872. [PubMed: 23723026]
25. Endeshaw Y. Clinical characteristics of obstructive sleep apnea in community-dwelling older adults. *J Am Geriatr Soc*. 2006; 54(11):1740–1744. [PubMed: 17087702]
26. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2014; 37(Suppl 1):S81–S90. [PubMed: 24357215]
27. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus--present and future perspectives. *Nat Rev Endocrinol*. 2012; 8(4):228–236. [PubMed: 22064493]
28. Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004; 27(5):1047–1053. [PubMed: 15111519]
29. Adeghate E, Schattner P, Dunn E. An update on the etiology and epidemiology of diabetes mellitus. *Ann N Y Acad Sci*. 2006; 1084:1–29. [PubMed: 17151290]
30. Narayan KM, Boyle JP, Geiss LS, et al. Impact of recent increase in incidence on future diabetes burden: U.S., 2005–2050. *Diabetes Care*. 2006; 29(9):2114–2116. [PubMed: 16936162]
31. Kalyani RR, Corriere M, Ferrucci L. Age-related and disease-related muscle loss: the effect of diabetes, obesity, and other diseases. *Lancet Diabetes Endocrinol*. 2014
32. Punjabi NM, Ahmed MM, Polotsky VY, et al. Sleep-disordered breathing, glucose intolerance, and insulin resistance. *Respir Physiol Neurobiol*. 2003; 136(2–3):167–178. [PubMed: 12853008]
33. Punjabi NM. Do sleep disorders and associated treatments impact glucose metabolism? *Drugs*. 2009; 69(Suppl 2):13–27. 13–27. [PubMed: 20047348]
34. Tasali E, Leproult R, Ehrmann DA, et al. Slow-wave sleep and the risk of type 2 diabetes in humans. *Proc Natl Acad Sci U S A*. 2008; 105(3):1044–1049. [PubMed: 18172212]
35. Stamatakis KA, Punjabi NM. Effects of sleep fragmentation on glucose metabolism in normal subjects. *Chest*. 2010; 137(1):95–101. [PubMed: 19542260]
36. Aurora RN, Punjabi NM. Obstructive sleep apnoea and type 2 diabetes mellitus: a bidirectional association. *Lancet Respir Med*. 2013; 1(4):329–338. [PubMed: 24429158]
37. Guilleminault C, Briskin JG, Greenfield MS, et al. The impact of autonomic nervous system dysfunction on breathing during sleep. *Sleep*. 1981; 4(3):263–278. [PubMed: 7302457]
38. Rees PJ, Prior JG, Cochrane GM, et al. Sleep apnoea in diabetic patients with autonomic neuropathy. *J R Soc Med*. 1981; 74(3):192–195. [PubMed: 7205856]
39. Catterall JR, Calverley PM, Ewing DJ, et al. Breathing, sleep, and diabetic autonomic neuropathy. *Diabetes*. 1984; 33(11):1025–1027. [PubMed: 6500185]
40. Mondini S, Guilleminault C. Abnormal breathing patterns during sleep in diabetes. *Ann Neurol*. 1985; 17(4):391–395. [PubMed: 4004160]
41. Ficker JH, Dertinger SH, Siegfried W, et al. Obstructive sleep apnoea and diabetes mellitus: the role of cardiovascular autonomic neuropathy. *Eur Respir J*. 1998; 11(1):14–19. [PubMed: 9543264]
42. Bottini P, Dottorini ML, Cristina CM, et al. Sleep-disordered breathing in nonobese diabetic subjects with autonomic neuropathy. *Eur Respir J*. 2003; 22(4):654–660. [PubMed: 14582920]

43. Nishimura M, Miyamoto K, Suzuki A, et al. Ventilatory and heart rate responses to hypoxia and hypercapnia in patients with diabetes mellitus. *Thorax*. 1989; 44(4):251–257. [PubMed: 2763226]
44. Weisbrod CJ, Eastwood PR, O'Driscoll G, et al. Abnormal ventilatory responses to hypoxia in Type 2 diabetes. *Diabet Med*. 2005; 22(5):563–568. [PubMed: 15842510]
45. Basu R, Breda E, Oberg AL, et al. Mechanisms of the age-associated deterioration in glucose tolerance: contribution of alterations in insulin secretion, action, and clearance. *Diabetes*. 2003; 52(7):1738–1748. [PubMed: 12829641]

Key Points

- Obstructive sleep apnea is associated with insulin resistance, glucose intolerance, and type 2 diabetes independent of confounding effects of age and obesity.
- Intermittent hypoxemia and sleep fragmentation in obstructive sleep apnea trigger a wide repertoire of pathophysiological mechanisms that may be responsible for altering glucose homeostasis and increasing the risk for type 2 diabetes.
- Treatment of obstructive sleep apnea is associated with improvements in daytime sleepiness, quality of life, and may also have a favorable impact on glycemic control and glucose metabolism.
- Obstructive and central sleep apnea are common in people with type 2 diabetes particularly in the presence of autonomic neuropathy
- Given the high prevalence of obstructive sleep apnea and type 2 diabetes in older adults, presence of one condition should prompt the evaluation of the other.

Figure 1.
Prevalence of obstructive sleep as a function of age.

Figure 2.
Associations and causal links OSA and metabolic abnormalities.

Figure 3.
Interactions between age, obstructive sleep apnea, and type 2 diabetes