To Sleep, Perchance to Breathe

Sleep Apnea, Snoring, and Sleep-Disordered Breathing

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Sleep apnea is defined as a sleep disorder with frequent episodes of upper-airway obstruction resulting in hemoglobin oxygen desaturation. The disorder is characterized by periods of breathing cessation (apnea) and periods of reduced breathing (hypopnea). Sleep apnea increases morbidity and mortality, thus making it a condition worthy of investigation.[1]

Sleep apnea is typically categorized as obstructive, central, or mixed. Central sleep apnea involves complete or partial lack of respiratory drive resulting from a lack of central nervous system initiation, combined with at least 10 seconds of absent respiration. This form of the disorder affects only 10 percent of patients with sleep apnea.[2] Obstructive sleep apnea (OSA) is the most common type and is characterized by a cessation of airflow despite respiratory effort, which is caused by obstruction in the upper airway. Mixed sleep apnea is a combination of lack of respiratory effort and obstruction in the upper airway. Sleep disordered breathing is a general category of sleep disorders that includes snoring, upper airway resistance syndrome, and OSA.

Prevalence

In industrialized countries, OSA affects approximately 4 percent of men and 2 percent of women.[3] OSA increases prevalence with age and studies suggest the disorder may be found in as many as 31 percent of elderly men and 19 percent of elderly women.[4] Children are also affected; studies demonstrate a prevalence of 0.7–3 percent, with a peak incidence in preschool-age children.[5] Many sources state that these numbers may be low as a result of the difficulty involved with, and cost of, definitive diagnostic procedures.[6]

Sleep apnea greatly affects the activities of daily living of both patients and their partners. Snoring, which may be a symptom or precursor to OSA, is common. Studies show that habitual snoring affects 29.5 percent of males and 8.9 percent of females. Snoring severity in 2.1 percent of females and 9.4 percent of males is significant enough to cause their roommates to leave the rooms shared with these patients.[7]

Risk Factors and Etiology

Studies have indicated that sleep apnea is more common in men and increases with age. In addition, it is more frequent in African-Americans than in whites.[8] Males over age 40 who are obese, smoke, or use alcohol are at increased risk for snoring and OSA.[7]

The strongest predictor for OSA is obesity. Studies show that the risk of OSA increases fourfold with an increase of the body–mass index (BMI) by 1 standard deviation. Neck circumference is also a strong predictor, suggesting that upper body or central obesity is more predictive than generalized obesity.[9] Hypothyroidism and menopause have also been associated with increased risk of OSA.[10,11]

There are a number of anatomical abnormalities and pathologies that can also lead to sleep apnea. Studies show that obese patients with OSA have an increase in the concavity of the posterior epiglottis. This change in shape is correlated with an increased BMI and with the severity of the airway collapse and OSA.[12]

Common symptoms of sleep apnea include fatigue, excessive daytime sleepiness, headache, and impaired thinking. Other symptoms are chronic snoring, depression, and personality changes.[2] Children frequently present with attention deficit, decreased intelligence, hyperactivity, and aggressiveness. Children rarely present with daytime sleepiness because apnea in children causes less awakening.[5] In addition, women tend to present more frequently than men with depression, insomnia, and hypothyroidism.[13]

Pathophysiology of Sleep Apnea

The obstruction present in OSA, the most common type of sleep apnea, can occur at multiple levels including the nasal cavity, the nasopharynx, and the tongue. A greater negative pressure is required to produce a given airflow volume when narrowing in these areas is present. Dilator muscles provide tone to the pharyngeal muscles to hold the airway open but are not sufficient to compensate for the closure of the airway in OSA. In addition, increased nasal resistance will increase the potential of collapse in the pharynx. Nasal obstruction often results from hypertrophy of the adenoids or palantine tonsils.[2]

Chemoreceptors within the brain decrease in sensitivity to carbon dioxide (CO_2) levels, so that even when CO_2 is raised, these receptors do not compensate properly by altering the rate and depth of lung ventilation. This results in a decrease in respiratory effort at a time when an increase is actually needed, leading to partial or total collapse of the airway and limited gas exchange in the lungs. Ultimately, this leads to a state of hypoxia and hypercapnia, which then increases the respiratory drive. Often, however, a severe hypoxic–hypercapnic state is required to stimulate a respiratory effort that is adequate to overcome the obstruction and end that particular event.

Specifically, the primary initiation for increased ventilation comes from chemoreceptors that are sensitive to the levels of CO_2 in the aortic arch, brainstem, and carotid bodies. In addition, changes in respiration cause changes in intrathoracic pressure, which have been shown to affect cardiovascular responses such as ventricular filling, venous return, and the release of atrial natriuretic peptide.[2]

Hypoxia and hypercapnia during an apneic episode also cause an increase in sympathetic nerve activity. This activation leads to many cardiovascular effects including increased peripheral resistance, vasoconstriction, and increased blood pressure. Interestingly, sympathetic nerve activity has been shown to increase in the daytime as well in patients with OSA. Studies suggest that this increase may be the cause of daytime hypertension and arrhythmias.[14]

Diagnosing Sleep Apnea

The severity of sleep apnea–hypopnea is measured by various methods. The number of apneas and hypopneas per hour of sleep can be evaluated with the Apnea-Hypopnea Index (AHI). In addition, the severity of oxygen desaturation during sleep can be measured via pulse oximetry or arterial blood gasses. The severity of daytime sleepiness, the most common symptom associated with apnea, can also be evaluated as sleep latency time using the Multiple Sleep Latency Test. An average sleep latency of less than 10 minutes indicates excessive sleepiness.

Sleep apnea is frequently underdiagnosed. It is estimated that 80–90 percent of OSA cases go undiagnosed.[15] Studies suggest that 30 percent of patients with essential hypertension have undiagnosed—and thus untreated—OSA.[16]

Diagnosis of OSA includes a thorough history and physical examination, using polysomnography to make the diagnosis definitive. The history should evaluate the occurrence of chronic snoring, excessive daytime sleepiness, and any medial condition associated with sleep apnea.

There are many questionnaires for assessing daytime sleepiness; in addition, sleep latency time can be measured. A physical examination should evaluate any anatomical abnormalities that might cause airway obstruction, such as enlarged adenoids, septal deviation, and nasal polyps. A fiberoptic endoscopy may be done to assess pharyngeal narrowing. Confirmation of the diagnosis is done with overnight polysomnography. Portable home devices used for diagnosis have been developed as a less-expensive alternative, although the assessments they do are slightly less definitive.[17]

Health Conditions Linked with Sleep Apnea

- Hypertension
- Atherosclerosis
- Tachycardia
- Bradycardia
- Ventricular ectopy
- Stroke
- Coronary artery disease
- Congestive heart failure
- Cor pulmonale
- Diabetes
- Gastroesopageal reflux disease
- Dementia
- Depression
- Aggressiveness
- Hyperactivity

Health Effects of Sleep Apnea

Sleep apnea often leads to extreme daytime sleepiness and other symptoms of sleep deprivation. And, sleep deprivation has been shown to increase accidents and accidental death. A study done using professional drivers demonstrated that the risk of automobile accidents increases significantly with frequent snoring and daytime sleepiness.[18] In addition to excessive sleepiness, sleep apnea can result in other problems.

Inflammation and Cardiovascular Disease

Sleep apnea increases the levels of many inflammatory markers, which may be one of the mechanisms by which it affects cardiovascular health. An example is C-reactive protein (CRP), an inflammatory marker correlated with atherosclerosis and coronary artery disease. A study performed on males with OSA showed a direct correlation between an increasing AHI and increasing CRP levels.[19]

In addition, proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α (TNF-α), have been shown to be elevated in patients with OSA.[20] The CD-40 ligand, which has been shown to be elevated in individuals with OSA, promotes proinflammatory mediators and is involved with atherosclerotic processes.[21] Treatment with nasal continuous positive airway pressure (nCPAP) decreases these inflammatory markers.[22]

Studies also indicate that individuals with OSA show increased platelet activity and aggregation, increased levels of fibrinogen and plasminogen activating factors, and a decrease in fibrinolytic functions.[23] Endothelial dysfunction also has been demonstrated, causing reduced endothelial-dependent vasodilation, while nCPAP therapy has been shown to improve nitric oxide release from the endothelium, improving the systemic endothelium-dependent vasodilation response.[24]

Cardiac Arrhythmias

Rates of both bradycardia and tachycardia are increased in individuals with sleep apnea. A large study performed on individuals with sleep apnea found that 48 percent had arrhythmias during nocturnal sleep.[25] In addition, it has been shown that there is a direct correlation between increased frequency of arrhythmias and an increasing number of apneic events as well as a higher degree of oxygen desaturation.[26] While awake, few of these individuals have

Risk Factors for Sleep Apnea

- Snoring
- Increased body–mass index
- Increased neck circumference
- Increasing age
- Male gender
- African-American ethnicity
- Smoking
- Alcohol use
- Menopause

cardiac arrhythmias, suggesting that the arrhythmias are caused by an increase in vagal tone and not by an anatomical disease process. Tracheo-stomy has reduced most of these arrhythmias.[25]

Other arrhythmias found more frequently in patients with sleep apnea include ventricular ectopy, ventricular tachycardia, premature ventricular contraction, atrioventricular block, and sinus arrest.[27]

Hypertension

Approximately 50 percent of individuals with OSA are also hypertensive, a correlation that also may be attributable to the effects of obesity on blood pressure (BP).[28] Studies indicate that severity of OSA is directly correlated with severity of both sleep apnea and daytime hypertension.[29] The increase in sympathetic activity caused by the induction of the fight-or-flight response is believed to be one contributing factor to the rise in BP. Treatment of OSA with nCPAP has been shown to decrease BP during both daytime and night-time hours.[30]

Sleep apnea is a risk factor for abnormal glucose metabolism, insulin resistance, and type 2 diabetes.

Strokes

OSA is an independent risk factor for the development of strokes or transient ischemic attacks.[31] Studies show that patients with untreated OSA experience more strokes and have higher rates of stroke morbidity and mortality than do patients who are treated with nCPAP.[32]

Diabetes

Sleep apnea is a risk factor for abnormal glucose metabolism, insulin resistance, and type 2 diabetes.[33,34] Treatment with nCPAP in individuals with OSA and type 2 diabetes has led to an increase in insulin sensitivity and a decrease in HbA1c levels.[35]

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) rates are increased in individuals with OSA. Studies show that the severity of GERD also increases with an increase in the AHI.[36] In patients with OSA, treatment of GERD has been shown to decrease the number of arousals during sleep.[37]

Psychiatric Conditions

Studies on veterans with sleep apnea showed an increase in psychiatric conditions compared to controls. A significant increase was found in mood disorders, such as depression, anxiety, dementia, psychosis, and post-traumatic stress disorder.[38] Studies indicate that treatment with nCPAP can reduce symptoms of depression.[39]

Children and Sleep Apnea

Children frequently present with different signs and symptoms of sleep-disordered breathing than adults. Children with OSA often have a low weight index, possibly the result of a decrease in growth hormone (GH) production. In part, this condition arises as a result of a relative failure to thrive; much as malnutrition contributes to a low weight index, a lack of oxygen to nourish the tissues limits growth of body tissues and makes a negative impact on the health of hormone-producing glands as well.

Insulin growth factor–1 and insulin growth factor–binding protein, both of which correlate with GH production, are lower in children with OSA. Other theories that explain the decrease in weight in children with OSA include anorexia or dysphagia caused by enlarged adenoids, and increased caloric use associated with increased respiratory effort.

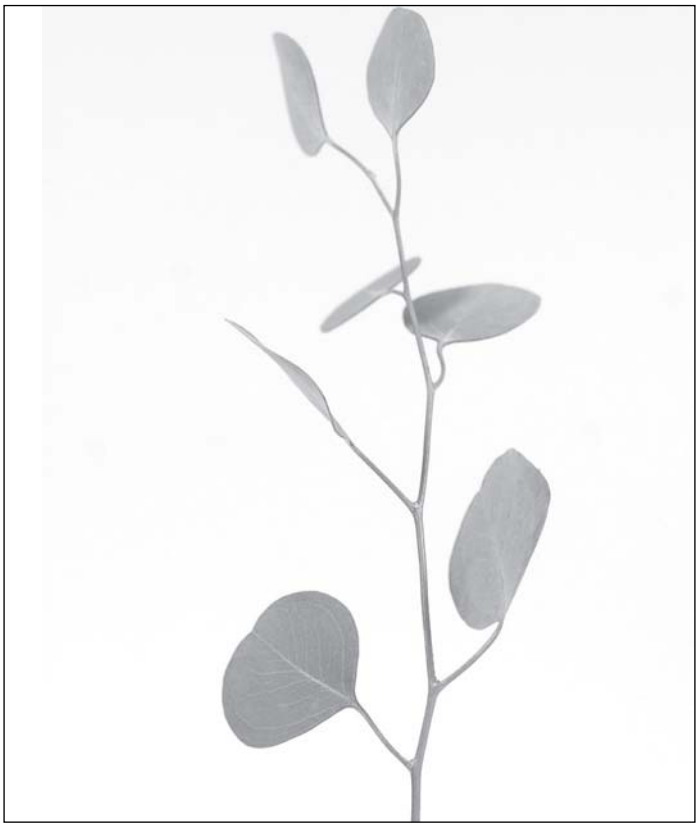
Children also tend to present with snoring, poor school performance, aggressiveness, and hyperactivity.[5] One study showed that 33 percent of children with attention-deficit hyperactivity disorder also had habitual nocturnal snoring.[40]

The most common cause of OSA in children is adenotonsillar hypertrophy. A study showed that 28 percent of children with adenotonsillar hypertrophy present with behavioral changes such as hyperactivity.[5]

Conventional Treatment for Sleep Apnea

Treatment of sleep apnea frequently entails use of nCPAP, bilevel positive airway pressure (BiPAP), oral appliances, or surgical procedures. The nCPAP provides positive pressure to prevent pharyngeal collapse, and is considered to be first-line treatment for moderate-to-severe apnea. Studies indicate that the nCPAP decreases the AHI by 60 percent.[41] Side-effects of the nCPAP include rhinorrhea, dryness, increased mucus production, and sneezing. Some 10–50 percent or more patients find nCPAP intolerable and discontinue using it.[41]

Oral appliances are used for mild sleep apnea and for individuals who are unable to tolerate or are noncompliant with the nCPAP. These appliances function by changing the position of the mandible or tongue. They have been shown to be less efficacious than nCPAP, but have better rates of compliance. Oral devices may cause tooth movement and occlusion changes with long-term use.[42]



Eucalyptus (*Eucalyptus globulus*).

There are many types of surgeries with varying efficacies for treating sleep apnea. Most procedures attempt to remove blockages to the airway or increase retrolingual space. Such procedures include uvulopalatopharyngoplasty, septoplasty, turbinectomy, midline glossectomy, maxillomandibular osteotomy, and tracheotomy.[2]

Alternative Treatments and Lifestyle Changes

Several lifestyle changes can make significant reductions in the severity of sleep apnea. Patients should be educated to sleep lying on one side. Weight loss is imperative, given the correlations of increased BMI and neck circumference with OSA. Even modest weight loss can be significant for reducing apnea symptoms; studies have shown that a 10 percent weight increase can cause a 32 percent increase in AHI, while a 10 percent weight loss could produce a 26 percent decrease in AHI.[43] Avoidance of alcohol and sedatives should also be encouraged.

Although specific studies on alternative treatments for sleep apnea are generally lacking, there are well-documented natural therapies that address the altered biochemistry and etiologic factors known to exist in sleep apnea. These therapies may prove important as adjunctive interventions, which are particularly important, given the well-documented poor compliance with nCPAP/BiPAP interventions and the invasiveness of many conventional options. Diet, nutritional supplements, and environmental modifications may improve sleep-disordered breathing.

Controlling inflammation and allergies is paramount in treating OSA. Allergies can cause an increase in adenoids and tonsil size as well as increasing mucous production, which can occlude the nasal airway.

N-Acetyl-Cysteine

N-acetyl-cysteine (NAC) is an acetylated ester of the amino acid L-cysteine. NAC has a significant ability to raise glutathione levels in the body (glutathione is a powerful antioxidant). NAC supplementation has been found to be more potent than glutathione itself. NAC is used to treat lung conditions as an expectorant and mucous thinner, and to produce anti-inflammatory effects.[44] Studies suggest that NAC decreases production of proinflammatory cytokines, such as TNF-α, which have been shown to be elevated in individuals with OSA.[45]

Essential Fatty Acids

Essential fatty acids (EFAs) cannot be made in the body and need to be consumed in the diet. Omega-3 fatty acids such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), and omega-6 fatty acids such as gamma-linolenic acid (GLA) are often taken as supplements to utilize their potent anti-inflammatory properties.

EPA and DHA are found in high levels in fish oils and provide both anti-inflammatory and antithrombotic effects. Specifically, EPA's cardioprotective effects include decreasing triglycerides, increasing high-density lipoprotein, and preventing arrhythmias.[46] EPA and DHA decrease inflammatory eicosanoids by competing with arachadonic acid (AA) in the lipo-oxygenase and cyclo-oxygenase pathways. Fish oils have been shown to decrease several proinflammatory cytokines as well.[47]

GLA is commonly found in borage (*Borago officinalis*) seed oil, evening primrose (*Oenothera biennis*) oil, and black currant (*Ribes nigrum*) oil. GLA decreases the inflammatory response by inhibiting the production of inflammatory leukotrienes from AA.[48]

Vitamin C

Vitamin C has many functions, including acting as both an antioxidant and an antihistamine. In a study performed on patients with OSA to test the theory that the endothelial dysfunction in this group is linked to oxidative stress, treatment with vitamin C improved endothelium–dependent vasodilation. This study suggests that antioxidant therapy should be considered for treatment of the cardiovascular dysfunction associated with OSA.[49]

Quercitin

Quercitin is a bioflavonoid frequently used to treat allergies because of its antihistamine, anti-inflammatory, and antioxidant effects. It is found in foods such as berries, brassica vegetables, apples, green tea (*Camellia sinensis*), onions, and red wine. Studies have demonstrated that quercitin inhibits the release of histamine from mast cells and basophils.[50] (Histamine is a chemical mediator responsible for allergy symptoms, such as constriction in the

lungs, congestion, and sneezing.) Absorption of quercitin is variable and may be improved by combining it with papain or bromelain.

Bromelain

Bromelain is a proteolytic enzyme derived from pineapples. This enzyme produces anti-inflammatory, fibrinolytic, and antiplatelet aggregation activities.[51] Studies show that bromelain interferes with the AA pathway, causing a decrease in inflammatory eicosanoid production.[52]

Eucalyptus

Historically, eucalyptus (*Eucalyptus globulus*) has been used for addressing many inflammatory respiratory complaints, including asthma and bronchitis.[53] Eucalyptus oil derived from the leaves and branches contains 60–90 percent of the constituent eucalyptol. Studies on eucalyptol show that it exerts strong anti-inflammatory, mucolytic, and analgesic effects. It inhibits the production of AA metabolites and such proinflammatory cytokines as TNF-α.[54]

Stinging Nettle

Stinging nettle (*Urtica dioica*) leaf contains vitamin C, vitamin E, carotenoids, calcium, potassium, and flavonoids such as quercitin and rutin. This herb has significant anti-inflammatory effects, and studies suggest that it may be beneficial for treating allergic rhinitis.[55] Researchers believe this may be the result of the nettles' quercitin content, which stabilizes mast cells and inhibits histamine release.[50]

Beefsteak Plant

The beefsteak plant (*Perilla frutescens*) contains several active ingredients such as rosmarinic acid and luteolin. Rosmarinic acid is a plant polyphenol found in the *Lamiaceae* genus of plants, which includes basil (*Ocimum* spp.), sage (*Salvia officinalis*), mint (*Mentha* spp.), rosemary (*Rosmarinus officinalis*), and perilla leaf.[56]

Oral supplementation using perilla leaves or extracts of rosmarinic acid has been shown to suppress allergic reactions.[57,58] A study confirmed that oral administration of perilla leaf extract inhibits production of TNF-α and decreases the allergic response and inflammation in mice.[59]

Another study demonstrated that perilla leaf extract enriched with rosmarinic acid is an effective treatment for patients who have seasonal allergic rhinoconjunctivitis.[58] Like rosmarinic acid, luteolin—found in various species of the perilla plant—is another plant flavonoid that has potent antiallergic properties.[59]

Licorice Root

Licorice (*Glycyrrhiza glabra*) is often used for gastrointestinal conditions such as GERD and ulcers. The finding that deglycyrrhizinated licorice (DGL) stimulates and/or accelerates the differentiation of glandular cells in the stomach—as well as stimulating mucous secretion—is of particular interest. This increased mucous secretion in the stomach is believed to account for at least part of licorice's beneficial properties. DGL also contains flavonoids that produce antimicrobial activity, including working against the ulcer-causing bacterium *Helicobacter pylori*.

Stinging nettle (*Urtica dioica*).

Basil (*Ocimum* spp.).

Rosemary (*Rosmarinus officinalis*).

It is important to treat GERD in individuals with sleep apnea because GERD can cause increased pharyngitis and sinusitis, exacerbating the apnea. Avoidance of caffeine, mints, chocolate, fatty or spicy foods, tomatoes, and alcohol is another way to decrease acid reflux. In addition, studies have shown that raising the head at night by raising the top of the bed may decrease nocturnal reflux.[60]

Methylsulfonylmethane and Hyaluronic Acid

Both methylsulfonylmethane (MSM) and hyaluronic acid are essential for maintaining connective tissue integrity, and thus for ensuring the rigidity and firmness of the underlying cellular matrix of the airway walls. MSM has been shown to have anti-inflammatory and antioxidant properties. Anecdotal evidence suggests that MSM may be effective for addressing many conditions, including snoring and allergic rhinitis.[61]

Hyaluronic acid, a glycosaminoglycan, could be considered for treatment of snoring and augmentation of airway connective tissue integrity.[62] Because of hyaluronic acid's viscoelastic quality, this substance may work to strengthen the connective tissue surrounding the airway and decrease obstructions.

Diet

Diet can affect inflammation and mucous production. Diets high in fruits and vegetables provide the vitamins and bioflavonoids that reduce allergy symptoms. Diets high in EFAs and low in animal products (such as dairy foods and meat) will decrease inflammation. (Animal products are high in AA and lead to an increase in inflammatory eicosanoids.) In addition, members of the nightshade family—such as potatoes, tomatoes, eggplants, and peppers—may also be proinflammatory in some individuals. Clinical observation suggests avoidance of mucous-forming foods such as dairy foods, bananas, and citrus fruits can be beneficial, although that line of thought is controversial.

Food allergies should also be considered when modifying the diet to decrease apneic episodes. Many individuals have latent food allergies that increase the inflammatory response and cause additional overall stress on the body. Many forms of testing are readily available to measure immunoglobulin (Ig)E and IgG antibodies to common foods.

Environment

Environmental allergies are important airway irritants. It is important to control allergies in order to minimize the nasal and pharyngeal congestion that can help compromise airway patency.

The best way to treat allergies is to advise patients to avoid the substances that trigger symptoms. The environment should be kept as free of potential allergens as possible. Pillows and mattresses should be covered with dust- and mite-proof covers. Bedding should be washed frequently in very hot water. Removal of carpets and items that collect dust in the bedroom may also help avoid dust and dust mites. Bathing and washing hair before bed also is suggested.

Mold anywhere in the home should be treated aggressively. Pets should be kept away from the sleeping areas and should be bathed regularly. High-efficiency particulate absorbing filters at home and work can improve air quality and decrease pollen exposure. Avoidance of cigarette smoke is recommended.

Anecdotal literature suggests other possible—though unproven—treatments for sleep apnea. Nasal sprays, nasal dilators, and magnetic mattresses and pillows are available.[63] Essential oil sprays and gargles to treat snoring have shown efficacy.[64] A case report also suggests hypnosis as an effective treatment for snoring.[65] Snoring has also been reduced by singing exercises in nonobese patients when done correctly and regularly.[66] Biofeedback training to control abnormal breathing while sleeping also has shown promising results. In at least one study, biofeedback reduced the duration of apneic episodes, resulting in higher oxygen saturation levels.[67]

Conclusions

Sleep apnea is a medical condition that warrants thorough study because of the increase in morbidity and mortality in patients who have the condition. It also affects quality of life greatly in many patients and frequently goes undiagnosed. If a patient complains of fatigue, excess sleepiness, lack of restorative sleep, or other unexplained systemic symptoms, a close review of the potential existence of apnea is a must. Given that sleep apnea can mimic and manifest as an accelerated peripheral vascular disease, the presence of premature vascular symptoms such as "classic shiny shin" may serve as a significant sign.

Although there are many treatments that have been proposed to help with sleep apnea, the best approaches remain weight loss and use of positive airflow therapy. Nonetheless, adjunctive therapies can help control the severity of apnea and snoring. □

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