Urological Manifestations of Obstructive Sleep Apnea Syndrome: A Review of Current Literature

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Introduction
Sleep apnea is defined to be an interruption of breathing during sleep lasting longer than ten seconds, which stimulates the sequence for chronic heart failure. It generates several mechanical, hemodynamic, chemical, and inflammatory changes, which negatively affects cardiovascular equilibrium of patients with heart failure [1]. In obstructive sleep apnea (OSA), respiration ceases when the muscles in the throat relax regardless of respiratory effort [1].

Pathophysiology
There are many practical pathophysiologic mechanisms that are impaired during the night. There are various components of OSA, including abnormal neuro-hormonal regulation, lack of physical activity, nutritional factors that can be involved in increased dietary sodium intake, and smoking of tobacco; which have all been correlated with blunted circadian rhythm of blood pressure [2]. OSA may increase trans-diaphragmatic pressure and decrease intra-thoracic pressure favoring Gastro esophageal reflux disease (GERD) [3]. Apnea may influence gastric dilation, decrease gastric emptying and influence transient lower esophageal sphincter relaxations [4]. Furthermore, greater respiratory effort increases the pressure gradient across the lower esophageal sphincter and eventually leads to GERD and its consequences.

Etiology
There are many disturbances that can result in a sleeping disorder, refer to Table 1 [5-11]. Obstructive sleep apnea severity can also be affected by multifactorial and specific symptoms in an individual such as upper airway anatomy, arousal threshold, upper airway muscle drive, and stability of the respiratory control system. Age contributes to the severity, with the likelihood of adults having upper airway collapsibility and younger patients...
commonly having alterations in ventilator control. Refer to Table 2 [12-19].

**Clinical manifestations of obstructive sleep apnea**

OA presents clinical symptoms in a variety of ways. Refer to Table 3 [20-24] for the clinical manifestations.

**Diagnostic methods of obstructive sleep apnea**

Polysomnography is a critical tool used to diagnose patients with OSA. In one study conducted by Fernandez Alonso et al., a questionnaire was used initially to get information from the patients and diagnose patients with OSA. Following the questionnaire, the results were confirmed using polysomnography [25]. Ustun et al. conducted a study to test a new method for diagnosing OSA known as SLIM, Supersparse Linear Integer Models. This technique was compared with 7 other state-of-the-art classification methods. Results concluded that SLIM is an accountable tool for OSA screening [26].

**Clinical manifestations of obstructive sleep apnea**

**Cardiovascular effects**

There are a variety of deleterious processes such as endothelial dysfunction, inflammation, platelet aggregation, and fibrosis, which provoke individuals to adverse cardiovascular events. There is evidence that OSA is significantly associated with cardiovascular disease which uses endothelial dysfunction as a mediating pathway [27].

**Cardiopulmonary effects**

Frequent arousals derive from upper airway obstruction, which consist of alveolar hypoventilation, altered arterial blood gases and acid-base status, and stimulation of the arterial chemoreceptors. These arousals are the cause of hypersomnolence, which are recurrent episodes of daytime sleepiness. Pulmonary and systemic hypertension can be caused by chronic intermittent alveolar and systemic arterial hypoxia-hypercapnia which affects the right and left ventricles and the renal system [4]. Noxious stimuli can activate the sympathetic nervous system, depress parasympathetic activity, provoke oxidative stress and systemic inflammation, activate platelets, and impair vascular endothelial function.

**Neurological effects**

Microvascular complications are associated with sleep apnea [28]. OSA is associated with reduced basal and functional capillary rarefaction with an additional risk of impaired peripheral perfusion. The mechanisms involved in this relation are most likely induced by the periodic hypoxia/reoxygenation that characteristically occur in OSA, which results in oxidative stress, endothelial dysfunction, and activation of the inflammatory cascade. On the other hand, the hypoxemia results in peripheral nerve damage by harming the vasanervorum in the early stages of ischemia, mechanisms to reduce peripheral neuropathy are activated, but these become insufficient over time, and obvious neuropathy is inevitable in chronic hypoxemia [29]. A correlation suggests a link between OSA and glaucoma or non-arteritic anterior ischemic optic neuropathy. This is believed to be secondary to direct hypoxia or optic nerve head vascular dysregulation. Patients with OSA are reported having papilledema and increased intracranial pressure. This is thought to be due to increased cerebral perfusion pressure and cerebral venous dilatation, secondary to hypoxia and hypercapnia [30]. There are not any correlations between the autonomic system and the neurobehavioral changes, which led to the belief that they have separate pathophysiological pathways [31]. There is an indirect link, which has been associated with OSA patients with nocturia, which consists of increased sympathetic levels and decreased parasympathetic levels [32]. OSA tends to coexist with autonomic regulatory dysfunction normally in the central region, which can damage the cardiovascular system and cause severe conditions [33]. It is unclear whether OSA is secondary to intracranial hypertension. Fleischman et al. examined the relationship between cerebrospinal fluid (CSF) rhinorrhea and OSA. Results found that patients with spontaneous CSF rhinorrhea were more

### Table 1 Factors resulting in sleeping disorders.

<table>
<thead>
<tr>
<th>Disturbances that lead to sleep disorders</th>
<th>References</th>
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<tr>
<td>Alcohol related</td>
<td>[5]</td>
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<tr>
<td>Major depressive and bipolar disorder</td>
<td>[6]</td>
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<tr>
<td>Psychiatric disorder</td>
<td>[7]</td>
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<tr>
<td>Traumatic brain injury</td>
<td>[8]</td>
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<td>Eating disorders</td>
<td>[9]</td>
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<td>Neurodegenerative disorders</td>
<td>[10]</td>
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<td>Bowel disorders</td>
<td>[11]</td>
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### Table 2 Risk Factors contributing to obstructive sleep apnea.

<table>
<thead>
<tr>
<th>Risk Factors of Obstructive Sleep Apnea Syndrome</th>
<th>References</th>
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<tr>
<td>Cardiovascular</td>
<td>[12,13]</td>
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<tr>
<td>Depression</td>
<td>[13]</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>[13,14]</td>
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<td>Obesity</td>
<td>[13,14]</td>
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<tr>
<td>Hypertension</td>
<td>[15]</td>
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<tr>
<td>Gender</td>
<td>[16]</td>
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<td>Age</td>
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<tr>
<td>Chronic Kidney Disease</td>
<td>[17]</td>
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<td>Hypoxemia</td>
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<td>Hyperlipidemia</td>
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<td>Increased Sympathetic Nerve Activity</td>
<td>[18]</td>
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<td>Metabolism</td>
<td>[19]</td>
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### Table 3 Clinical manifestations of obstructive sleep apnea.

<table>
<thead>
<tr>
<th>Clinical Symptoms of Obstructive Sleep Apnea Syndrome</th>
<th>References</th>
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<tr>
<td>Snoring</td>
<td>[20]</td>
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<td>Daytime somnolence</td>
<td>[21]</td>
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<td>Nasal</td>
<td>[22]</td>
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<td>Mouth dryness</td>
<td>[23]</td>
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<td>Nocturia</td>
<td>[24]</td>
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likely to be diagnosed with OSA. Spontaneous CSF rhinorrhea is known to cause intracranial hypertension, and patients should be screened for spontaneous CSF rhinorrhea relating to OSA [34]. Bakhsheshian et al. reviewed cases of spontaneous CSF leaks, and found a connection with OSA, through increased intracranial pressure. However, further studies need to be conducted to evaluate the relationship between OSA and spontaneous leaks [35].

**Metabolic effects**

Impaired glucose metabolism is associated with obese patients with OSA [36]. Night hypoxia is correlated with glucose levels, which shows that it has an effect on glucose metabolism with OSA patients [37]. Glucose tolerance impairment and pancreatic beta-cell function is associated with OSA, but insulin sensitivity is due to obesity [18,38]. Vitamin D deficiency can play a role in glucose metabolism in patients with OSA [39]. OSA is accompanied by increased hormonal levels such as adrenocorticotropic hormone, which leads to alterations in tissue [40]. These alterations eventually end up disturbing the feedback mechanisms to regulate hormonal levels [41]. Studies have shown that Bisphenol A, which disturbs the endocrine system, has an important function in the pathogenesis of OSA [42].

**Psychological effects**

Depression is the most prevalent psychological effect for patients dealing with OSA. Bjorndottir et al. sought to determine prevalence of depression among patients with OSA using psychiatric interview. The results of the interview concluded that mild depression was more prevalent among women than men. However, major depression had no significant differences among sexes. Depression and OSA are believed to be dependent on one another in these patients, and assessment tools should test for both to improve diagnostic accuracy [43]. Patients dealing with insomnia are at risk for suicidal ideation, all due to OSA. Choi et al. conducted a study to determine the prevalence of suicidal thoughts among OSA patients, using a questionnaire. The study found the severity of insomnia was positively correlated with depressive mood and suicidal ideation. There was significant association between OSA and suicidal ideation, additional to insomnia [44].

**Urological Manifestations of Obstructive Sleep Apnea**

**Renal**

There is a high risk for chronic kidney disease that is associated with patients who have severe OSA without hypertension or diabetes [45]. Hypoxemia and sleep fragmentation are correlated with OSA, which leads to activation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system, cardiovascular hemodynamics alteration, and causes free radical generation. This can lead to endothelial dysfunction, inflammation, platelet aggregation, atherosclerosis, and fibrosis, which can predispose individuals to cardiovascular events such as renal damage and proteinuria through hemodynamic changes, ischemic stress, and intermediary condition such as hypertension [46]. Renal transplants can heal patients, but there is a prominent probability of the patient developing OSA in the post-operative stage [47]. End-stage renal disease (ESRD) is believed to increase the severity of OSA due to the reduced upper way area and the destabilization of ventilator control, which creates a cycle that causes OSA fluid overload disorders such as congestive heart failure and ESRD [48]. ESRD also contributes to the pathogenesis of OSA and treatment by ultrafiltration reduces the effects of OSA without altering uremic status [49]. ESRD patients seem to show a correlation with leg fluid volume and left atrial size, which is also linked to OSA severity [50]. Renal vasodilation and endothelial dysfunction are characteristics of OSA [51].

**Neurogenic bladder**

Sporadic hypoxia in OSA patients results in oxidative stress which can lead to alterations in bladder, detrusor instability, and spontaneous contractions through the activation of cell survival signaling from OSA [52]. There is a 95% ratio that patients with bladder pain syndrome/interstitial cystitis also have OSA [53]. Patients with benign prostatic enlargement who frequently awake from sleep to urinate might possibly have OSA [54]. An increasing manifestation of overactive bladder and urgency incontinence in males is correlated with an increasing severity of OSA [55]. Nocturnal urination is also correlated with OSA severity, excessive daytime sleepiness, and coronary artery disease [56]. Bladder function may be damaged during chronic obstructive sleep apnea hypopnea syndrome [57].

**Frequency**

Patients with severe OSA reported nocturnal urination three times more frequently than those with moderate OSA [58].

**Prostate**

OSA induces systemic inflammatory processes, which can damage tissue and lead to prostatic enlargement. This can lead to an increased risk of benign prostate hyperplasia development, which is age dependent [59].

**Nocturia**

Nocturia is a very common and severe disorder because of the effects it has on patients [60]. In OSA patients, nocturia is a strong independent predictor of hypertension [61]. Nocturnal urination is also correlated with OSA severity, excessive daytime sleepiness, and coronary artery disease [56,62]. The analysis of a 24 hour urine collection provides constructive data on the pattern of water and solute excretion, which could aid in determining the underlying mechanism of nocturia and monitor treatment [63]. Hypoxemic children with OSA exhibit enuresis of antidiuretic hormone, which is associated with polyuria and nocturia [64]. Atrial natriuretic peptide increases sodium and water excretion which leads to the inhibition of other regulatory hormonal systems such as fluid volume, vasopressin, and renin-angiotensin-aldosterone complex [65]. Nocturnal enuresis and OSA tend to be common conditions during adolescence, which is accompanied with bedwetting due to OSA severity [66]. Nocturnal enuresis severity increases as severity of OSA increases, especially in female children [67].
Sexual Manifestations of Obstructive Sleep Apnea

Males

OSA in males is recognized as an underlying pathogenic factor to sexual dysfunction [68]. Males with sexual dysfunction tend to have higher systolic blood pressure and TNF-alpha [69]. Sexual dysfunction severity in aging men is due to modifiable risk factors [70]. There are many sexual dysfunctions in men that seem to be linked such as erectile dysfunction (ED), low dyadic, and solitary sexual desire, which share many risk factors. There are other factors that are unique to each and they should be addressed before any other outcome is reached. ED factors include increasing age, depression, body fat mass, and hypertension. Unique factors for solitary sexual desire include absence of partner, lower education, income, unemployment and migration, whereas low dyadic unique factors include lower plasma testosterone [71]. There is a direct relationship between erectile dysfunction, vascular dysfunction, neurobehavioral cognitive function and endothelial dysfunction [72]. Endothelial dysfunction is the pathophysiological mechanism that links OSA to ED. There is strong evidence that suggests OSA independently causes endothelial dysfunction which is linked to ED [73]. Inflammatory cytokines, chemokines, and adhesion molecules induce endothelial dysfunction [74]. Surgical and nonsurgical treatment of OSA is correlated with alleviating sexual dysfunction [75]. ED patients that were treated with continuous positive airway pressure (CPAP) saw positive improvements after three months [76]. Oral appliances can be an alternative method of treatment for erectile dysfunction of OSA induced ED patients [77]. Studies have shown that sildenafil is a better alternative treatment for erectile dysfunction of OSA induced ED patients [78].

Obesity and OSA share many similar sexual manifestations. One in particular is male infertility. Katib et al. reviewed the links between obesity and male infertility. The publications reviewed indicate that impaired spermatogenesis resulted from hypotestosteronaemia defects [79]. Torres et al. [80] and Hirotsu et al. [81], conducted studies in mice mimicking sleep apnea and found intermittent hypoxia could lead to reduced fertility.

Sleep-related painful erection is a rare disorder that is identified with painful nocturnal erection, a correlation between REM sleep and pain, and an absence of pain during sexual activity [82]. Citalopram is effective at reducing sleep-related painful erection due to the regulation of neurotransmitters involved in erection [83].

Hypogonadism

OSA is associated with a decrease in pituitary-gonadal function [84]. Clinical presentation varies due to the time of onset of androgen deficiency. Defects can occur from a disorder in testosterone production or spermatogenesis, genetic factors, or androgen therapy. Hypogonadism is determined on the basis of consistent signs and symptoms of androgen deficiency and low morning testosterone levels [85]. It is suggested that in males, sleep rhythm is linked to the androgenic hormonal profile, but not to the chronobiological diurnal rhythm [86]. Low testosterone levels are strongly associated with fatigue in OSA patients [87]. CPAP therapy has reversed the effects of OSA by increasing testosterone in patients with low testosterone, bringing them back to normal levels. It has also improved many other hypogonadism symptoms such as fatigue and depression [88]. Hypoxemia also plays a role in decreased testosterone levels in patients with OSA [89]. Studies have shown that testosterone therapy aggravates OSA symptoms at 6-7 weeks, but not after 18 weeks, which can be due to ventilator chemo reflexes changes [90].

Females

Female sexual dysfunction (FSD) is defined when the sexual cycle is impaired due to stress. In premenopausal women, FSD and OSA are correlated only when nocturnal hypoxia is present [91]. OSA is correlated with sexual dysfunction, but there is no correlation between the severity of OSA and the severity of sexual dysfunction [92]. OSA in females corresponds with premenopausal and postmenopausal women. Progesterone is what connects sexual dysfunction to OSA in premenopausal women [93]. Changes in the prolactin secretion in OSA patients is thought to be correlated with hypoxic stress and subsequently to result in reversible changes with continuous positive airway pressure (CPAP) therapy [94]. OSA can alter circulating placenta-secreted glycoproteins and markers of angiogenesis in pregnant women [95]. OSA is associated more with glucose intolerance in premenopausal women than postmenopausal women. Improving lifestyle can improve nocturnal hypoxia, which can allow glucose homeostasis [96]. It has been reported that female patients with OSA have seen improvements in sexual dysfunction after a year of CPAP treatment [97]. Post menopause stages and waist size are correlated with the severity of OSA. Reducing the circumference of the waist can reduce OSA symptoms [98]. Postmenopausal women can be diagnosed with a very common condition called polycystic ovary syndrome (PCOS), which causes high androgen levels, low estrogen levels, and is correlated with OSA [99]. Women with polycystic ovary syndrome (PCOS) tend to develop OSA, which in turn can lead to the development of nonalcoholic fatty liver disease [100]. There are two main types of PCOS, the two types consist of PCOS with OSA and PCOS without OSA [101]. Studies have shown that women with PCOS with OSA are often obese, and that obesity should be looked at as the prime factor for the development of OSA [102]. PCOS is usually accompanied by certain characteristics such as insulin resistance, glucose intolerance, and type 2 diabetes, which can be linked to the onset of OSA [103].

Treatments

Non-Invasive treatment

Positive airway pressure is an effective method for treating patients with moderate and severe OSA [104]. The gold standard treatment for OSA is nasal continuous positive air pressure, which is correlated with improving sexual functioning and improving quality of life [68]. CPAP is suggested to be capable of reversing the effects of OSA induced sexual dysfunctions [105].
CPAP is associated with improving reduced cerebral glucose metabolism in the precentral gyrus and cingulate cortex [106]. CPAP therapy can decrease the excretion of nocturnal atrial natriuretic peptides and improve motility of the detrusor of the bladder [57]. CPAP therapy can also reduce excretion of urinary albumin [107]. CPAP therapy is effective at decreasing daytime fatigue and sequelae of untreated OSA [108]. Long term CPAP treatment does not have any effects on testosterone or estradiol levels [109]. Adaptive servo-ventilation efficiently decreases sleep apnea. Left ventricular ejection fraction and other aspects of life qualities are improved within six months of treatment [110]. Supplementation treatment exhibited improvement to the glucose metabolism and inflammation [39]. Renal sympathetic denervation is associated with significantly reducing severity in OSA [111]. In mild OSA cases, nonsurgical treatments such as CPAP are first line therapy [112].

Invasive treatment

Upper airway surgery can improve the quality of sleep in patients with OSA [113]. Mandibular advancement is another surgical procedure that seems to be effective in treating OSA [75]. Surgery improves clinical outcomes, systolic blood pressure, lipid profile, and increases the number of endothelial progenitor cells, which are correlated with endothelial impairment [114]. Removal of tonsils and adenoids leads to significant improvements. Adenotonsillectomy is considered to be first line therapy in severe OSA [112]. Multilevel surgery targeting the retropalatal and tongue-base was effective in reducing mean platelet volume and apnea hypopnea index. Mean platelet volume is known to be predictors of cardiovascular diseases, hypertension, and stroke [115]. Surgery is effective at improving overnight polysomnography in obese children [116].

Summary

Obstructive sleep apnea (OSA) syndrome carries significant morbidity and mortality, frequently associated with obesity. Urological manifestation of OSA, as related to lower urinary tract symptoms and male and female sexual dysfunction are discussed. Non-invasive and invasive treatment options are outlined.

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Compliance with Ethical Standards

The authors declare they have no conflict of interest.
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