Sleep Medicine Reviews 69 (2023) 101787

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

"Nocturia and obstructive sleep apnea syndrome: A systematic review"

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ARTICLE INFO

Article history:
Received 17 January 2023
Received in revised form
1 April 2023
Accepted 23 April 2023
Available online 29 April 2023

Handling Editor: M Vitello

Keywords:
LUTS
Urology
Apnea hypopnea index
CPAP
OSAS

ABSTRACT

Lower urinary tract symptoms represent a significant public health problem worldwide, impairing patients' quality of life, especially in elderly people. Among LUTS, nocturia is assessed as the most experienced entity related to several disorders such as sleep disorders and/or obstructive sleep apnea syndrome (OSAS).

Among OSAS patients, nocturia stands as a bothersome symptom that increases alongside with the OSAS severity. However, despite the nocturia and OSAS shared a long-acknowledged link, the causes, and the pathophysiology for development of nocturia in OSAS have remained largely unexamined. Generally, the patients with OSAS experienced nocturia due to easy waking or increased bladder filling. However, nor the effect of treatment on management of nocturia in OSAS patients are well-established.

1. Introduction

Lower urinary tract symptoms (LUTS) represent a significant public health problem worldwide, impairing patients' quality of life, especially in elderly people [1,2]. Among LUTS, nocturia is assessed as the most experienced entity defined as "complaint of waking at night to void from the time of falling asleep to the time of intending to rise for the next day" [1–4]. Nocturia can be caused by several disorders: inflammation, benign prostatic hyperplasia, overactive bladder, neurogenic dysfunctions, sleep disorders, obstructive sleep apnea syndrome (OSAS) [5–7].

Among OSAS patients, nocturia stands as a bothersome symptom that increases alongside with the OSAS severity [6,8–10]. Indeed, Oztura et al. reported the prevalence of nocturia to be 52%–76.9% in a large cohort of patients, occurring in nearly 50% of patients with OSAS [11]. However, despite the nocturia and OSAS shared a long-acknowledged link, the causes for development of nocturia in OSAS have remained largely unexamined. Generally, the patients with OSAS experienced nocturia due to easy waking or increased bladder filling [8,11]. To the best of our knowledge, no previous authors had analyzed the current available literature to consolidate the observations on these linked conditions and to create solid evidence to manage the disease. Additionally, we investigated how the relationship between nocturia and OSAS could be modified from medical and surgical treatment for those conditions.

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https://doi.org/10.1016/j.smrv.2023.101787
1087-0792/

2. Materials and methods

We designed a systematic review according to the "Preferred Reporting Items for Systematic Reviews and Meta Analyses" (PRISMA) statement (Fig. 1) [12].

This protocol was registered in PROSPERO (ID= CRD42022368888).

2.1. Literature search

The search was performed in the Medline (US National Library of Medicine, Bethesda, MD, USA), Scopus (Elsevier, Amsterdam, The Netherlands), and Web of Science Core Collection (Thomson Reuters, Toronto, ON, Canada) databases up to August 2022. No chronological restrictions were applied. The following keywords were combined to capture relevant publications with a title/abstract search: ("OSAS" OR "sleep apnea" OR "obstructive sleep apnea") AND ("lower urinary tract symptoms" OR "LUTS" OR "nocturia" OR "nicturia"). Reference lists in relevant articles were also screened for additional studies.

2.2. Selection criteria

Two authors (L.N. and M.A., a senior and a junior urologist resident, respectively) reviewed the records separately and individually selected relevant publications, with any discrepancies resolved by a third senior author (E.C. an associate Professor). An initial screening of titles and abstracts was performed to determine which papers could meet the inclusion criteria. Subsequently, the full-text articles underwent a more exhaustive assessment. PICOS (Population, Intervention, Comparison, Outcome, Study design) criteria were used to assess the eligibility of studies [13]. PICOS criteria were set as follows: (P) Patients with OSAS experienced nocturia and patients with nocturia screened for OSAS; (I) Continuous Positive Airway Pressure (CPAP); (C) None; (O) The correlation between OSAS and nocturia, predictors of severity of nocturia in OSAS patients, predictors of severity of OSAS in nocturia patients; (S) Prospective, retrospective primary studies, case series, case reports, case-control, observational and comparative studies were included. Abstract, letters to the editor, editorial comments, systematic reviews and meta-analysis, narrative reviews and original articles without primary data were excluded. Ethical approval and patient consent were not required for the present study.

2.3. Data Collection

The following data were extracted: first author, year of publication, sample size, study design, age, sex, body mass index (BMI), comorbidities, data concerning the diagnosis of OSAS (medical history defined as "medical interview", questionnaires such as Epworth Sleepiness Scale [ESS] or Berlin questionnaire or STOP-BANG test, polysomnography [PSG]), data concerning the diagnosis of nocturia ("medical interview", International Prostatic Symptoms Score [IPSS], International Consultation on Incontinence Modular Questionnaire-Nocturia [ICI–N], Nocturia, Nocturnal Enuresis, and Sleep-interruption Questionnaire [NNES-Q], Overactive Bladder Symptom Score [OAB-SS], Sleep Disordered Breathing-Nocturia Model [SDB-NM], Urinary Distress Inventory-6 [UDI-6]), medications, apnea/hypopnea index (AHI), Respiratory Disturbance Index (RDI), oxygen saturation (defined as the lowest value recorded during the PSG), nocturia (defined as pathological when experienced $\geq$ twice for night). Moreover, among patients with OSAS underwent treatment (CPAP or TORS) we collected the following variables (Table 2): first author, year of publication, number of OSAS patients, follow-up duration, ESS values, AHI, oxygen saturation, time spent <90% saturation, nocturia frequency, night-time urinary volume, IPSS and nocturnal polyuria index (NPi), defined as the fraction of 24-h urine output produced during the intended sleep period (nocturnal urine volume/24-h urine volume) after and before treatment, respectively [14].

2.4. Quality assessment

The evaluation of the level of evidence was performed according to Oxford Center for Evidence-Based Medicine 2011 [15]. The methodological index for non-randomized studies (MINORS) was used to assess the methodological quality of both comparative and non-comparative studies (Supplementary Tables 1–2) [16].

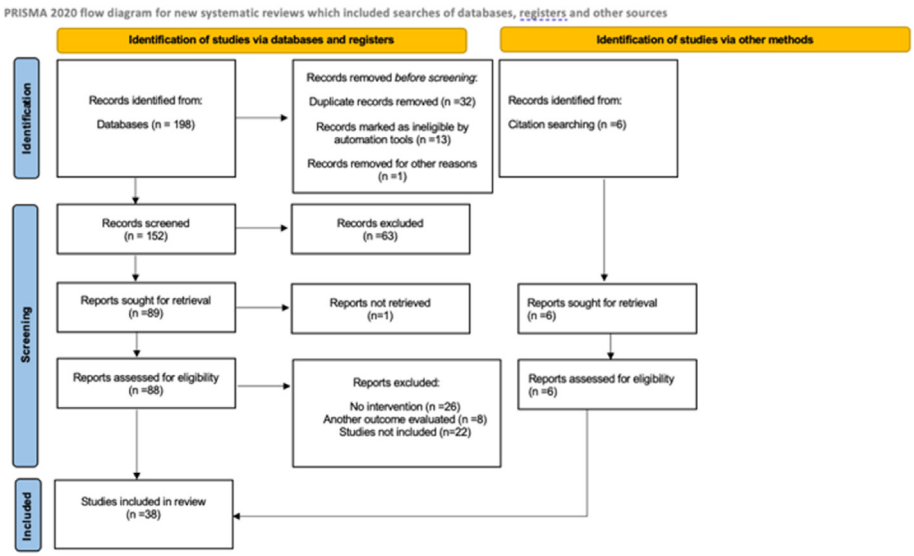

Fig. 1. PRISMA 2020 flow diagram for tnew systematic reviews which included searches of databases, registers and other sources.

2.5. Data analysis and synthesis

As a relatively low number of relevant papers with high heterogeneity methodology were expected, quantitative data were reported as found in the original studies. Percentages and medians were used to pool the extracted data. The main findings of the included papers were also summarized qualitatively.

3. Results

The search strategy revealed a total of 202 results. Screening of the titles and abstracts revealed 116 papers eligible for inclusion. Further assessment of articles, based on full text, led to the exclusion of 78 papers. A total of 38 papers (13 retrospective studies, 5 cross-sectional studies, 2 Community-based study, 18 prospective studies), involving a total of 42625 patients (27–22674) divided in 29225 men (68.6%)1, 13400 and women (31.4%), plus 225 (0.5%), without available data of gender, were included in the final analysis.

Study characteristics and patients' clinic-demographic profile were reported in Table 1. The patients have a mean age of 53.3 years, in three papers the median was reported to the place of the mean. Age is not available in three papers. BMI of patients varied between 23.7 and 45.8 (mean: 28.9) kg/m^2, in five papers there was no data about BMI, in two papers only the median was reported.

Dyslipidemia was the most frequent comorbidity reported (n=8291, 19.47 %). 2219 (5.21 %) patients were affected by hypertension (HT), 6182 (14.51 %) subjects had cardiovascular disease (CVD), 4392 (10.31 %) type II diabetes mellitus (DM2), 3468 (8.14 %) gastro-esophageal reflux disease, 3074 depression (7.21 %), 1826 (4.28 %) chronic obstructive pulmonary disease, 763 (1.79 %) stroke, 615 (1.44 %) benign prostatic hyperplasia (BPH), 163 (0.38 %) overactive bladder (OAB), 93 (0.02 %) other psychiatric conditions, 162 (0.38 %) erectile dysfunction, 71 (0.16 %) restless legs syndrome, 71 (0.17 %) menopause, 63 (0.14 %) Parkinson disease, 61 (0.14%) chronic kidney disease, 50 (0.11 %) cancers, 35 (0.08 %) other neurologic disorders, 33 (0.08 %) asthma, 32 (0.07 %) periodic limb movement disorder, 29 (0.06%) lung disease, 22 (0.05 %) Osteoarthritis, 21 (0.05 %) Dementia, 14 (0.03 %) insomnia, 13 (0.03 %) gastro-intestinal disorders, 10 (0.02 %) urge urinary incontinence, and 10 (0.02 %) other disease not well defined. Comorbidities was not available in 6107 patients (14.34%).

Data concerning medications was not available in 24 papers (63.1%). When cited, the most used medications were diuretics used 527 times, alpha-blockers 209 times, antidepressant 61 times, anticholinergics 48 times, hypnotics 36 times, 5α-reductase inhibitors 32 times, not specified antihypertensive drugs 27 times, angiotensin-receptor blockers 26 times, benzodiazepines 23 times, beta-blockers 21 times, insulin or antidiabetics 17 times, angiotensin-converting enzyme inhibitors 15 times, acetaminophen 14 times, H2 antagonist and IPP ten times, acetylsalicylic acid seven times, thyroid replacement drugs five times, anticonvulsants five times and coumadin four times.

Overall, nocturia affected 19703 patients (46.27%), while 19757 patients reported no nocturia (46.39%), no data were available for 3124 (7.33 %).

The AHI mean value among 24 papers is 30.4, one paper only divided AHI value under or over 30, no data were available in 11 papers, in two papers only the median was reported. The RDI mean value among six papers is 58.78, no data were available in 32 papers. About oxygen saturation, the lowest value reported is 24.4 %, the mean value is 73.7 among ten papers, no data were available in 27 papers, in one paper only the median was reported.

Diagnosis of OSAS was made according to different strategies: PSG was used 31 times, ESS ten times, medical interview twice, Berlin Questionnaire twice, STOP-BANG test once. Conversely, no data were available in three papers.

Diagnosis of nocturia was made according with different strategies: IPSS questionnaire was most used tool (14 times), medical interview seven times, OAB-SS six times, OAB-v8 twice, ICIQ-N twice, Dry Time Sense'R Strip once, ICI–N once, urination diary once, NPI once, not well specified questionnaire once, 3-day bladder diary once, Transabdominal-ultrasonography once, NNES-Q once, UDI-6 once, and ICIQ-SF once.

The pre- and post-treatment (CPAP or surgery for OSAS) characteristics were mentioned only in 12 (31.5%) papers, including 713 patients. The mean of AHI pre-treatment and post treatment was 22.1 and 16.4, respectively. No data were reported in 6 articles. The mean of nocturic frequency pre-treatment and post treatment was 4.1 and 2.1, respectively. No data were reported in 2 articles. The mean value of night-time urine volume (calculated as the difference between the pre- and post-treatment values) was 166.12 mL. The mean of IPSS pre-treatment and post treatment was 7.3 and 4.8, respectively. No data were reported in 5 articles.

To sum up, across the sample, 14178 (33.2%) of OSAS patients experienced nocturia (**Table 3**). Data were not available in 27 papers. Furthermore, 409 (0.9%) nocturia patients screened for OSAS were affected by the disease. In 29 papers, data were not available.

According to MINORS criteria, only 7 (18,4%) studies were qualitatively satisfying (with a global score of 16), while 16 (42,1%) studies were just below the threshold (Supplementary Tables 1–2).

4. Discussion

The relationship between nocturia and OSAS was long studied during last decades [17–21]. Indeed, Fitzgerald et al. assessed the role of AHI as an independent predictor of frequency of nighttime urination, with a dose-dependent manner [22]. Despite this, the relationship remains still unclear. To the best of our knowledge, no previous authors had analyzed the current available literature to consolidate the observations on these linked conditions. Our analysis provided interesting points of view.

4.1. The role of age and BMI in the onset of nocturia

Historically, patients' age and BMI were the established risk factors for OSAS [8,23–29]. Our analysis showed that almost a one third of OSAS patients experienced nocturia but <1% of nocturia patients have OSAS. Moreover, the mean of age was 53.3 years, with one third of papers including middle-aged patients. As previously demonstrated, Kang et al. showed that age and the BPH predicted the presence of pathological nocturia in young and middle-aged men [33]. No association between age and nocturnal voiding were found in elderly patients [33]. Similarly, Coban et al. demonstrated that among 50 patients with sleep apnea, there were 44% of patients that woke at least three times to urinate at night compared to patients without sleep apnea (only 5%) [1]. Conversely, Endeshaw et al. found higher frequencies of nocturnal urination among older adults affected by severe OSAS with no statistically significant difference between AHI and nocturia [34]. Thus, OSAS had a minimal impact on nocturia in elderly patients and the two conditions were unrelated [34,35]. In agreement with Deger et al. and Tuncer et al., OSAS severity did not have a meaningful relationship with nocturia while age and BMI scores were established risk factors for the bothersome urinary symptoms [19,23,36]. Specifically, OSAS patients could be affected by pathological nocturia. According to the patients' age the association between OSAS presence and the symptom changes, weakening from the middle-age to the elderly. This evidence maybe suggests an evolutive and multifactorial influence on urinary functioning, regardless the

Table 1
Study characteristics and patients' clinic data extracted from 38 papers included in the review.

Author	Sample size	Type of study	Age (mean, SD) *years*	Sex *women, men*	BMI (mean, SD) *kg m-2*	Comorbities	Diagnosis of OSAS *Questionare, PSG*	Diagnosis of nocturia *Interview, Questionnaire*	Medications *Yes/No/Drug, number*	AHI (mean, SD)	RDI (mean, SD) *events/ hour*	Oxigen saturation (*Lowest value recorded [%]*)	Nocturia (≥ twice for night) *number of patients*
Ayik 2014 [41]	730	PS	**Mild**: 50.0, 10.9 **Moderate**: 53.2, 15.2 **Severe** 50.5, 10.2	59 W 101 M 42 W 86 M 60 W 222 M	30.6, 4.9 31.0, 5.0 33.3, 6.1	570, OSAS 478 HT, 513 DM, 498 CVD, 568 COPD	ESS, PSG	Questionnaire	N/A	N/A	N/A	N/A	372
Arslan 2018 [20]	139	RS	**Mild** 50, 39-58 **Severe** 52, 37-60	139 M	26.1, 4.0 26.9, 2.8	N/A	PSG	IPSS Trans abdominal-US	N/A	12, 6-14 54, 31-65	N/A	N/A	N/A
Bing 2012 [40]	150	CCS	[a]66, IQR: 60-81	100 W 50 M	26.4 (24.9 −27.9)	20, HT 1, DM 3, CVD 6 Neurological disorders	ESS PSG	Interview	5, Hypnotics	6.1 (3.5 −8.8)	N/A	24.4 (13.1 −35.8)	75
			[a]72, IQR:2-82		25.3 (23.4 −27.2)	2, HT 2, DM 1, CVD 4, Neurological disorders			1, Hypnotics	13.8 (7.1 −20.5)		35.0 (13.5 −56.5)	
Bliwise 2004 [36]	27	CSS	N/A	11 W 16 M	N/A	Dementia, 21 HT, 13 GID, 13 Neurologic disorders, 25 BPH, 2 CVD, 19 Cancer, 3 LD, 5 Other, 10	PSG	Dry Time Sense'R Strip	CV, 15 Acetaminophen, 14 Antidepressant, 8H2antagonist/IPP, 10 Diuretics, 7 Insulin or antidiabetics, 6 ASA, 7 Thyroid replacement, 5 Anticonvulsants, 5 Coumadin, 4	N/A	54.6, 46.2	N/A	N/A
Chen 2011 [10]	65	CSS	62.6, 11.5	25 W 40 M	23.9, 3.4	7, Stroke 25, HT 10, DM 26, CVD	Interview, ESS, PSG	Urination diary, NPI	14, Hypnotics 5, Antidepressant	AHI<30, 29	N/A	N/A	36
			69.6, 9.9		25.0, 3.7	11, stroke 30, HT 19, DM 34, CVD			9, Hypnotics 8, Antidepressant	AHI ≥ 30,36			
Chung 2022 [43]	1264	PS	61.6, 11.4	306 W	25.7, 4.6	N/A	PSG ESS	N/A	N/A	25.2, 20.9	N/A	84.3, 7.5	520
			55.1, 13.3	958 M	27.0, 4.4					36.5, 24.7		81.8, 8.4	
Chuang 2022 [54]	123	PS	42.8, 9.5	123 M	N/A	N/A	ESS PSG	IPSS OABSS	N/A	42.14, 22.03	75.08, 11.82	91.52, 68.38	N/A
Coban 2020 [1]	54	PS	47.06, 11.15	54 M	30.61, 3.83	37, BPH 27, ED	N/A	IPSS	N/A	50.71, 19.12	N/A	N/A	28
Deger 2021 [23]	125	RS	49.9, 11.6	27 W 98 M	N/A	68, OAB 55, HT 38, DM	PSG	OAB-V8 ICIQ-SF	N/A	**Mild** 8.1, 2.9 **Moderate** 24.0, 9.3 **Severe** 55.8, 10.6	N/A	N/A	N/A
Deger 2021 [30]	124	RS	49.9, 11.6	27 W 97 M	31.4, 6.1 21.1, 6.3	55, HT 38, DM 100, CVD	PSG	3-day bladder diary	N/A	36.5, 25.8 37.5, 26.8	N/A	N/A	92
Destors 2015 [6]	22674	PS	57.47, 12.86	6199 W 16475 M	31.84, 6.68	1252, COPD 4636, CVD, 703, Stroke 3468, GERD, 3114 DM, 7751 Dyslipidemia 3062, Depression	ESS, PSG	Interview	N/A	39.20, 19.53	N/A	N/A	12237
Fernandez-Pello 2021 [24]	43	PS	59.63, 8.67	14 W 29 M	32.4, 54	13, DM 25, Dyslipidemia 8, CVD 25, HT	PSG	IPSS	2, alpha blockers 11, antidiabetics 21, anti hypertensive	N/A	N/A	N/A	N/A
Finamore 2018 [18]	275	PS	65, 12	106 W 169 M	32.4, 5,8	16, DM 6, COPD 50, HT 32, CVD 5, Ashtma 66, Dyslipidemia 6, BPH	N/A	N/A	24, Diuretics 15, ACE-i 26, SARTANI 20 BetabLockers 8, Alpha-blockers	[1]24, IQR: 9-45	N/A	N/A	66
	196	RS	N/A		N/A	N/A	PSG	N/A	N/A		N/A		N/A

FitzGerald 2006 [22]				100 W 96 M						[1]23.8, IQR:4.3 −116		[1]83, IQR:58-93	
Guilletminault 2004 [29]	88	PS	68, 3.2	88 M	29.8, 3.1	N/A	ESS PSG	N/A	N/A	49, 11	N/A	75, 5	31
Kang 2012 [27]	1757	RS	50.1, 11.4	1757 M	25.75, N/A	65, BPH 421, HT 117, DM 38, CVD	NPSG	Interview	Yes, 243	27.7, 22.6	N/A	81.8, 8.49	266
Kaynak 2004 [8]	1075	RS	49, 11	246 W 829 M	30, N/A	227 HT, 64 CVD, 61 DM	PSG	N/A	Yes, N/A	N/A	33, 29	81, 11	370
Irer 2018 [3]	126	PS	42.0, 7.1	126 M	29.1,4.3 28.9, 2.8 33.6, 5.9	70 ED	PSG	IPSS OABS-V8	N/A	10.5,3.1 24.4,3.9 59.4,25.5	N/A	N/A	N/A
Lowenstein 2008 [35]	31	RS	[a]65, IQR: 39-81	N/A	[a]28, IQR 20-39	16, OAB	PSG	ICI−N	N/A	15.1 (1.6 −43)	N/A	N/A	21
Margel 2006 [53]	97	PS	55, 12	22 W 75 M	33, 7	22, CVD 16, DM	PSG	IPSS	22, Diuretics or Digoxine	N/A	34, 24	72, 21 78, 12.3	N/A
Martin 2016 [25]	708	CBS	60.7, N/A	708 M	28.6, 4.5	25, CVD 93, Pshychiatric conditions 28 AshtmaED, 65 24, BPH 19, Cancer 22, OSteoarthritis 14 Insomnia	PSG	IPSS	75, α -adrenoblockers 37, Anti-cholinergics 88, diuretics 32, 5α-reductase inhibitors	N/A	N/A	N/A	207
Metta 2017 [48]	131	RS	63, 8.5	131 M	35, 5.8	32, CVD 81, HT 6, Stroke 43, DM 107, BPH	ESS, PSG	N/A	23, BDZ	35.6, 27.3	N/A	N/A	107
Miyauchi 2015 [49]	92	PS	55.0, 10.8	8 W 43 M	26.8, 3.6	N/A	PSG	IPSS OAB-SS ICIQ-N	N/A	48.0, 25.9	75.6, 10.5	N/A	N/A
Miyazaki 2015 [37]	666	PS	68.3, 11.5	286 W 380 M	23.8, 3.9	422, HT 227, DM 433, Dyslipidemia 492, CVD	PSG	N/A	N/A	N/A	80.4, 7.4	N/A	561
Miyazato 2017 [50]	40	PS	56.90, 14.1	7 W 33 M	28.4, 4.2	8, DM 22, HT 16, Dyslipidemia 3, Stroke 4, CVD 3, Depression	ESS PSG	IPSS OABSS ICIQ-NQOL	N/A	56.8, 28.1	N/A	N/A	N/A
Miyauchi 2020 [21]	90	RS	56.0, 12.0	19 W 71 M	25.5, 4.0	N/A	PSG	IPSS OABSS	N/A	26.5, 26.3	N/A	83.0, 9.4	N/A
Myer 2020 [42]	130	RS	[a]54, IQR: 40−66	130 W	[a]27.7, IQR: 24.2 −34.9	44, HT 17, DM 71, menopause	Berlin questionnaire STOP-BANG	NNES-Q, UDI-6	24, Diuretics 7, Anticholinergic 36 Antidepressant	N/A	N/A	N/A	38 30
Niimi 2016 [17]	104	PS	63.4, 11.7	18 W 86 M	26.3, 4.5	45, HT 36, DM 10, Stroke 25, BPH 7, CVD 20, CKD	PSG	IPSS OAB-SS	N/A	34.7, 18.9	N/A	N/A	78
Oztura 2006 [11]	1970	PS	N/A	461 W 1509 M	N/A	N/A	PSG	N/A	N/A	3.81, 5.54	5-15 337	88.78, 4.64	N/A
										10.10, 8.29	15-30 576	86.49, 5.55	
										47.74, 26.09	>30 1012	74.96, 11.50	
Parthasarathy 2012 [38]	6342	PS	64.2, 10.5	3361 W 2981 M	28.7, 5.5	231, DM	PSG	Interview	345, Diuretics 123, alpha blockers	4.6, 1.6	N/A	N/A	3625 (2030 M)
Park 2016 [56]	37	RS	45.0, 12.3	9 W 28 M	27.1, 3.9	12, HT 1, DM	PSG	IPSS OABSS	N/A	33.3, 24.7	N/A	N/A	N/A
Tandeter 2011 [7]	341	CSS	65.9, 5.8	341 M	26.4, 3.6	341, BPH	Berlin questionnaire	Interview	N/A	N/A	N/A	N/A	75
Tuncer 2016 [19]	194	CSS	**Mild** 44.40,9.66 **Moderate** 45.22, 12.41 **Severe** 47.41, 10.46	N/A	29.58, 4.37 29.74, 3.48 32.34, 5.36	79, OAB 10, UUI	PSG	IPSS	N/A	28.55, 28.18	N/A	N/A	74

(*continued on next page*)

Table 1 (*continued*)

Author	Sample size	Type of study	Age (mean, SD) *years*	Sex *women, men*	BMI (mean, SD) *kg m-2*	Comorbities	Diagnosis of OSAS *Questionare, PSG*	Diagnosis of nocturia *Interview, Questionnaire*	Medications *Yes/No/Drug. number*	AHI (mean, SD)	RDI (mean, SD) *events/ hour*	Oxigen saturation (*Lowest value recorded [%]*)	Nocturia (≥ twice for night) *number of patients*
Vaugan 2013 [39]	39	PS	63.6, 9.8	26 M 13 W	28.3, 4.4	63, PD 19, HT 4, DM	PSG	N/A	N/A	6.3, 8.3	N/A	N/A	12
Vrooman 2019 [51]	274	PS	60.3, 0.7	84 W 190 M	N/A	N/A	N/A	Interview	17, Diuretics 1 Alfa blockers 4 anicholinergic 1 mirabegron	N/A	N/A	N/A	206
Yoshimura 2009 [44]	2241	CBS	58.3, N/A	1176 W 1065 M	23.7, N/A	145, HT 67, DM 23, Stroke 86, CVD 39, Renal disease 22, LD 28, Cancer 71, RLS 32, PLMD	Interview, ESS	IPPS, IPPS QoL score	N/A	N/A	N/A	N/A	546
Yue 2009 [45]	28	PS	7.9, IQR: 6.2–9.8	10 W 18 M	N/A	N/A	PSG	N/A	N/A	17.36, 2.61	N/A	78.34, 13.44	N/A
Yu 2019 [52]	35	RS	59.8,11.7	8 W 27 M	26.8, 9.1	28, HT 8, DM 8, BPH 9, Depression 2, CKD 3, CVD	PSG	Interview	6, anti-hypertensive 7, hypnotics 4, anti-depressants	42.9, 16.7	N/A	73.7, 12.3	30

AHI: apnea-hypopnea index; ASA: acetylsalicylic acid; AUA-SS: American Urological Association symptom score; BDZ: benzodiazepine; BMI: body mass index; BPH: benign prostatic hyperplasia; CBS: community-based study; CCS: case-control study; CVD: cardiovascular disease; CSS: cross-sectional study; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; DM: diabetes mellitus type II; ED: erectile dysfunction; ESS: Epworth Sleepiness Scale; GID: gastro-intestinal disorder; HT: hypertension; ICI–N: International Consultation on Incontinence Modular Questionnaire-Nocturia; IPP: proton pump inhibitors; IPSS: International Prostatic Symptoms Score; IQR: interquartile range; LD: lung disease; MAP index: multivariable apnea prediction; GERD: gastro-esophageal reflux disease; MSA-P: multiple system atrophy-parkinsonism; NIS: non interventional study; NNES-Q: Nocturia, Nocturnal Enuresis, and Sleep-interruption Questionnaire; NPI: nocturnal polyuria index; NPSG: nocturnal polysonnography; OAB: overactive bladder; OAB-SS: Overactive Bladder Symptom Score; OSAS: obstructive sleep apnea syndrome; PBS: population-based study; PD: Parkinson disease; PLMD: periodic limb movement disorder; PS: prospective study; PQS: prospective questionnaire study; PP: postpolio patients; QoL: quality of life; RDI: respiratory disturbance index; RLS: restless leg syndrome; RS: retrospective study; SD: standard deviation; SDB-NM: Sleep Disordered Breathing-Nocturia Model; SRQ: self-reported questionnaire; TORS: transoral robotic surgery; UDI-6: Urinary Distress Inventory-6; US: ultrasonography; UTI: urinary tract infections; UUI: urge urinary incontince

[a] When mean and SD of the variable considered were not available, the median and IQR were reported for completeness.

presence of OSAS. Indeed, the reason could be related to the structural and functional changes of the urinary system (such as the reduction of bladder capacity and voiding due to hypotonia of detrusor muscle) that could impair the urinary function [5,34]. Moreover, a decrease in the glomerular filtration rate, an increased risk of CVD, physiological changes in the lower urinary system, and BPH in men can additionally explain the occurrence of nocturia in older age [5,9,23,30].

Furthermore, for every BMI increase of 5, risk of severe LUTS increased by 13% as previously assessed [30]. We found an average BMI of 28.9 ("overweight"), with more than half of papers regarding patients with a BMI > 25. The exact relationship between increased BMI and nocturia remains unclear, despite several hypotheses have been advanced: nocturia may be associated with increased nocturnal urine production due to overeating and fluid consumption or increased intra-abdominal pressure [24,30–32]. As a results, both age and an unfavorable BMI could result in nocturia, especially in OSAS patients.

4.2. The role of comorbidities in the onset of nocturia

OSAS is a multifactorial disease related to patients' metabolic profile, such as DM2, obesity, and metabolic syndrome (MS) [30,37–42]. Moreover, Otzura et al. strengthened this evidence and noticed that also age, HT, and AHI scores were significantly associated with nocturia [11]. According to literature data, we could consider the intermittent hypoxia (IH) condition (shared by DM2, obesity, and MS) as one of the potential causes for nocturia in OSAS patients [11,43]. However, we should remark that IH is not necessarily present in these diseases. Therefore, Abler and Vezina highlighted the causal association between LUTS (specifically nocturia) and the conditions above that often occurred along with OSAS, regardless of influences [30]. In our analysis, we summarized that the most frequent comorbidity was dyslipidemia (19.47%), followed by CVD, HT and DM2. Additionally, our rate of OSAS patients presenting nocturia is 33.2% but results were underestimated; indeed, less than half of papers reported data regarding OSAS patients that experienced nocturia. According to our result, the metabolic profile impairment could be a shared pathway by the comorbidities above, including OSAS. However, several larger studies with a wider OSAS sample are needed to confirm or reject this hypothesis.

4.3. Physiopathology of nocturia in OSAS patients

The pathophysiological mechanisms that connect OSAS and nocturia are not entirely understood but several intriguing hypotheses were postulated. Starting from OSAS, disease-related hallmarks are represented by intermittent hypoxia (IH) or periodic exposure to reduce blood oxygen [17,24,30]. As a result, the sleep fractionation with the breathing pauses may cause the arousal of patients [17,30]. This arousal could determine the need of patients to urinate [30,44]. Specifically, the IH of OSAS patients caused by the obstruction to airflow during the sleeping resulted in reduction of intrathoracic pressure [5,17]. Consequently, the pressure gradient increases the venous return to the right atrium that expands [17]. At the same time, the IH activates the sympathetic nervous system, leading to a vasoconstriction and increasing blood pressure [6,30,33]. The vasoconstriction of pulmonary arteries contributes to increase the level of hypoxemia [30,33]. The dilation of the atrium results in an increased secretion of atrial natriuretic peptide (ANP) that stimulates the excretion of sodium and thus the water excretion [17,30,45]. These effects are implemented by the brain natriuretic peptide (BNP) secreted in response to the central nervous hypoxemia and hypercapnia [18,23,30,45]. Moreover, both ANP and BNP inhibit the secretion of antidiuretic hormone (ADH)

Table 2
Characteristic of apnea and nocturia in OSAS patients pre and post treatment.

				PRE-TREATMENT								POST-TREATMENT							
Author	OSAS Patients *number*	Follow up period (mo)	Type of treatment	ESS	AHI (mean, SD)	Oxigen saturation (*Lowest value recorded [%]*)	Time spent <90% saturation	Nocturic frequency (% or number of episodes mean SD)	Night-time urine volum (mL)	IPSS	NPi	ESS	AHI (mean, SD)	Oxigen saturation (*Lowest value recorded [%]*)	Time spent <90% saturation	Nocturic frequency (% or number of episodes mean SD)	Night-time urine volume (mL)	IPSS	NPi
Chou 2015 [48]	14	N/A	CPAP	N/A	26.8, N/A	N/A	N/A	23	N/A	N/A	N/A	N/A	7.4, N/A	N/A	N/A	10	N/A	N/A	N/A
Chuang 2022 [54]	123	3	TOR	8.61+-4.44	42.14+-22.03	75.08+-11.82	N/A	N/A	N/A	6.46+-5.60	N/A	6.87+-3.81	25.93+-21.42	84.04+-7.78	N/A	N/A	N/A	5.03+-4.88	N/A
Coban 2020 [1]	54	3	CPAP	N/A	N/A	N/A	N/A	1.92 +- 1.51	N/A	10.38 +-8.26	N/A	N/A	N/A	N/A	N/A	1.24 +- 1.21	N/A	7.2 +-6.65	N/A
Deger 2021 [23]	48	3	CPAP	N/A	N/A	N/A	N/A	2.3 +- 1.4	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.7 +- 2.2	N/A	N/A	N/A
Deger 2021 [30]	125	3	CPAP	N/A	N/A	N/A	N/A	2.6 +- 1.7	567.7 +-486.6	N/A	N/A	N/A	N/A	N/A	N/A	2.4 +- 2.4 +- 2.7	380 +-329.5	N/A	N/A
Fernandez-Pello 2021 [24]	43	12	CPAP	N/A	N/A	N/A	N/A	1.38 +- 1.2	485.11 +-271.04	10.48 +-7.66	28.4	N/A	N/A	N/A	N/A	0.49 +- 0.69	406.63 +-383.33	7.69 +-7.04	24.5
Irer 2018 [3]	126	3	CPAP	N/A	N/A	N/A	N/A	2.1 +- 1.3	547.0 +-285.5	8.4 +-6.3	N/A	N/A	N/A	N/A	N/A	0.5 +- 0.5	95.6 +-107.8	2.8 +-2.5	N/A
Miyauchi 2015 [49]	51	1	CPAP	N/A	51.5 +-28.7	76.4 +- 7.9	N/A	2.0 +- 1.1	542.4 +-289.9	5.9 +-4.7	N/A	N/A	3.4 +-2.3	90.0 +- 4.1	N/A	1.0 +- 1.2	354.0 +-217.4	4.8 +-4.6	N/A
Miyazaki 2015 [37]	32	3–6	CPAP	N/A	45.3 +-13.6	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2.5 +-3.7	N/A	N/A	N/A	N/A	N/A	N/A
Miyazato 2017 [50]	40	3	CPAP	8.3 +-5.1	56.8 +-28.1	N/A	N/A	2.1 +- 1.2	723.3 +-498.4	7.6 +-5.5	37.0 +-16.2	6.1 +-3.8	N/A	N/A	N/A	1.2 +- 1.1	453.6 +-251.4	5.0 +-4.3	28.6 +-14.7
Niimi 2016 [17]	22	N/A	CPAP	N/A	N/A	N/A	N/A	2.0 +- 1.7	N/A	2.4 +-1.2	0.46 +-0.13	N/A	N/A	N/A	N/A	0.9 +- 1.1	N/A	1.6 +-0.9	0.35 +-0.17
Yu 2019 [52]	35	3, 7, 14, and 28 days	CPAP	7.6 +-3.3	42.7 +-16.2	73.6 +- 9.6	N/A	1.9 +- 1.4	668.1 +-314.5	N/A	N/A	10.2 +-5.8	43.0 +-17.3	73.7 +- 12.3	N/A	2.2 +- 1.3	847.0 +-341.8	N/A	N/A

AHI: apnea hypopnea index; CPAP: Continuous Positive Airway Pressure; ESS: Epworth Sleepiness Scale; IPSS: International Prostatic Symptoms Score; MO: months; N/A: not available; NPi: nocturnal polyuria index; TOR: trans-oral surgery.

Table 3
Summary of total sample size categorized in four main categories: patients with OSAS, patients with nocturia, OSAS patients experienced nocturia and patients with nocturia resulted positive at the screening for OSAS.

Author	Sample size	Patients with OSAS *number of patients (%)*	Patients with Nocturia *number of patients (%)*	Patients OSAS experienced Nocturia *number of patients (%)*	Patients with Nocturia resulted positive at the screening for OSAS *number of patients (%)*
Arslan 2018 [20]	139	113 (81.2)	N/A	N/A	N/A
Ayik 2014 [41]	730	570 (78)	N/A	679 (93)	N/A
Bing 2012 [40]	150	N/A	75 (50)	N/A	22 (14.6)
Bliwise 2004 [36]	27	N/A	N/A	22 (81.4)	N/A
Chen 2010 [10]	65	N/A	N/A	N/A	36 (55.3)
Chuang 2022 [54]	123	123	N/A	47	N/A
Chung 2022 [43]	1264	1264 (100)	N/A	520 (41.1)	N/A
Coban 2020 [1]	54	54 (100)	N/A	28 (51.8)	N/A
Deger 2021 [23]	125	125 (100)	N/A	N/A	N/A
Deger 2021 [30]	124	124 (100)	N/A	92 (88.4)	N/A
Destors 2015 [6]	22654	N/A	N/A	12240 (53.9)	N/A
Fernandez-Pello 2021 [24]	43	N/A	N/A	N/A	N/A
Finamore 2018 [18]	275	N/A	66 (24)	N/A	32 (11.6)
FitzGerald 2006 [22]	196	N/A	N/A	N/A	N/A
Guilletminault 2004 [29]	88	60 (68.1)	N/A	N/A	N/A
Irer 2018 [3]	126	104 (82.5)	N/A	23 (18.2)	N/A
Kang 2012 [27]	1757	1301 (74)	N/A	N/A	108 (6)
Kaynak 2004 [8]	1075	846 (78.6)	N/A	370 (34.4)	N/A
Lowenstein 2008 [35]	31	N/A	21 (67.7)	N/A	17 (54.8)
Margel 2006 [53]	97	N/A	N/A	N/A	N/A
Martin 2016 [25]	708	N/A	207 (29.2)	N/A	65 (9.1)
Metta 2017 [48]	131	107 (81.6)	N/A	83 (63.3)	N/A
Miyauchi 2015 [49]	92	63 (68.4)	N/A	N/A	N/A
Miyauchi 2020 [21]	90	20 (22.2)	N/A	N/A	N/A
Miyazaki 2015 [37]	666	N/A	561 (84.2)	N/A	91 (13.6)
Miyazato 2017 [50]	40	40 (100)	N/A	N/A	N/A
Myer 2020 [42]	130	130 (100)	N/A	N/A	N/A
Niimi 2016 [17]	104	N/A	78 (75)	N/A	16 (15.3)
Oztura 2006 [11]	1970	N/A	N/A	N/A	N/A
Park 2016 [56]	37	37 (100)	N/A	N/A	N/A
Parthasarathy 2012 [38]	6342	N/A	N/A	N/A	N/A
Tandeter 2011 [7]	341	N/A	75 (21.9)	N/A	N/A
Total Score	42625	5289	1872	14178	409
Tuncer 2016 [19]	194	159 (81.9)	N/A	74 (38.1)	N/A
Vaughan 2013 [39]	39	N/A	37 (94.8)	N/A	N/A
Vrooman 2019 [51]	274	N/A	206 (75.1)	N/A	N/A
Yoshimura 2009 [44]	2241	N/A	546 (24.3)	N/A	22 (0.9)
Yu 2019 [52]	35	21 (60)	N/A	N/A	N/A
Yue 2009 [45]	48	28 (58.3)	N/A	N/A	N/A

from the supraoptic and paraventricular nuclei of hypothalamus and the renin-angiotensin-aldosterone complex, resulting in augmentation of diuresis [23,45]. It will be interesting to study how the effects of IH could be reduced or blocked at the urinary system, avoiding the nighttime urination needs. From our analysis, only one paper treated the hypothesis in comprehensive vision [30]. We should notice that 5.21% of patients collected were affected by HT, related to sodium retention [46]. If salt excretion is insufficient

during the daytime, patients excrete salt at night according to Guyton's concept of the pressure-natriuresis curve [46]. As result, urine must be produced, and consequently nocturnal polyuria leads to nocturia condition [46]. Moreover, we must mention that medications such as diuretics (thiazide or loop) are used in the HT management [46]. In our review, diuretics were used 527 times. Thus, a cross sectional effect due to medications and comorbidities could be the responsible of a complex physio-pathological mechanism of nocturia in OSAS patients.

4.4. The role of treatment for OSAS in the management of nocturia

The analysis collected fascinating results relative to the effect of the OSAS treatment on the nocturia. Several previous authors had investigated how CPAP could mitigate the nocturia in OSAS patients [1,47–53]. Importantly, CPAP represents the first-line treatment for OSAS patients that do not present tonsils or adenoids enlargement, nasal polyps and/or facial deformities [54]. The CPAP machine ensures a continuous stream of air through a mask worn over the nose; the positive pressure of the forced air keeps the airways open, and the breathing is not hampered [50,51,55]. Instead, the surgery represents a second-line treatment for patients who are not suitable for CPAP machines [56,57]. As a result, both CPAP therapy and surgery have been shown to improve urinary symptoms [3,22,23,37,48–51,58]. According to Hu et al. 23 Chinese patients with nocturia were diagnosed with OSA following a sleep study [59]. These patients also presented a bladder dysfunction revealed by urodynamic studies: an increased pressure build up and sensitivity to bladder filling, and weak bladder detrusor muscle contractions [59]. Following three months of CPAP therapy, frequency of nighttime urination decreased, while bladder muscle contraction improved [59]. Moreover, a recent study of 123 OSAS patients undergoing *trans*-oral robotic surgery (TORS) assessed the role of this innovative technique on the reduction of daytime symptoms (both respiratory and urinary) and polysomnographic parameters [54]. Indeed, Chuang et al. measured a statistically significant improvement of LUTS and IPSS at three months follow-up after TORS-OSA surgery, both for mild/moderate OSAS and severe OSAS group patients [54].

From the analysis emerged that less than one third of papers measured the effects of OSAS treatment on nocturia and only six papers (15.7%) reported almost all the pre and post treatment variables studied. Moreover, concerning the variable of interests, the AHI post treatment decreased about six points compared to pre-treatment value. The nocturic frequency post treatment resulted halved compared to pre-treatment value. These data were corroborated by previous evidence [60]. Indeed, Wang et al. demonstrated a reduction of 2.28 relative to the mean number of nocturia incidents similarly to ours. Moreover, the mean night-time urine volume differences were 183.12 mL, like ours to 166.13 mL. Respect to Wang et al., our sample is double. This observation reflects how the role of CPAP was robust in the treatment of nocturia episodes in OSAS patients. Indeed, CPAP treatment eliminates negative intrathoracic pressure, relieving the obstruction of the airways. The pathophysiological mechanism of natriuresis was stopped and the nocturia was mitigated. However, information of the long-term efficacy (> of 6 mo of follow-up) and the absence of urinary impairment after CPAP suspension in OSAS patients experienced nocturia are missing in the studies analyzed.

4.5. Strengths and limitations

The strengths of this study are the sample size, the methodology and the number of variables collected to describe comprehensively the conditions studied. Despite these some limitations should be discussed: firstly, the major limitation derives from the low methodological quality of available data and the retrospective nature of the study. Indeed, the data recorded must be validated in larger prospective studies. Moreover, the papers enrolled in the final analysis presented a high heterogeneity in the sample about the gender, the age, the race and the diagnosis of the diseases mentioned above. It should be noted that an important lack of data was present referring to the medical treatments. Indeed 24 papers (63.1%) did not report information on the pharmacological intake of the patients. Finally, a remarkable limitation was the lack of information about daytime and nighttime fluid intake could influence the significance of the "nocturia" and urine volumes.

In conclusion, in this review, we have summarized compelling evidence that highlights the overwhelming links between OSAS and LUTS, nocturia specifically. We have discussed a host of possible pathophysiologic factors that bind the two diseases and have highlighted gaps in knowledge, focusing on the effect of OSAS treatment on nighttime voiding.

Taken together, OSAS and nocturia are two entities strictly related. In the presence of OSAS, urinary symptoms are often more severe, occurring in a dose- dependent manner. The severity of OSAS and the nocturia occurrence could negatively impact on patients' QoL [61,62]. Our review showed as age, BMI and AHI scores and HT are also significantly associated with nocturia. Further, treatment of OSA with CPAP therapy simultaneously confers improvements in LUTS. Thus, physicians could focus on the evaluation of these aspects when they visit both OSAS and LUTS patients. For example, Urologists should consider and investigate silent OSA disorders when they visit patients with persistent nocturia, despite the used treatment (alpha adrenergic blockers), and without a clear sign of bladder outlet obstruction. It would be useful also to reduce the medication taken by a patient with multiple comorbidities. While the medical field is hyperspecializing, these observations emphasize how the contemporary patients must be included in multidisciplinary team. Every professional figure could simplify the management of patients with more than two comorbidities who could present non-specific symptoms, ensuring the best diagnostic and therapeutic options.

Practice point

The knowledge of relationship between OSAS and nocturia may be helpful to:

- Monitor the severity of OSAS and reducing the dose-dependent effect, controlling the risk factors of nocturia in OSA patients such as age, BMI and AHI scores.
- Candidate patients to a treatment for OSAS that simultaneously confer improvements in LUTS, reducing the use of drug in patients with multiple comorbidities.
- Create specific multidisciplinary team to better manage patients' diagnosis and treatment, reducing the distress of "waiting for a diagnosis" and ensuring the best diagnostic and therapeutic options.

Research agenda

In the future we need to be able to not only predict the diagnosis of OSAS in patient that experienced nocturia, but also which patients:

- Are at the highest risk of morbidity and whether this risk can be modified by treatment.
- Obtain the most significant improvement in both diseases, reducing the health expenditure and the distress of patients and increasing their quality of life.
- Are eligible to new further personalized therapy.

Data availability statement

My manuscript has no associated data.

Fundings

No funding was received for this research.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

For this type of study formal consent is not required.
This article does not contain any studies with human participants performed by any of the authors.

Declaration of competing interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2023.101787.

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