Mini Review – Voiding Dysfunction

Nocturia: The Complex Role of the Heart, Kidneys, and Bladder

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**Abstract**

We review the role of the heart, kidneys, and bladder in the pathophysiology of nocturia and nocturnal polyuria. Lower urinary tract symptoms such as nocturia have often been associated with lower urinary tract dysfunction. It is known that the bladder contributes to nocturia in the case of low functional capacity, urgency, and detrusor overactivity. Heart diseases, especially arterial hypertension and congestive heart failure, are closely related to nocturnal polyuria. The main mechanisms include renal hyperfiltration and elevated atrial natriuretic peptide. A number of drugs frequently used in cardiovascular disorders are implicated in nocturia; diuretics, calcium channel blockers, and \(\beta\)-blockers induce nocturnal polyuria and thus nocturia, whereas alpha-blockers improve nocturia. Among the different forms of hypertension, nondipping arterial hypertension has been associated with a higher risk of nocturnal polyuria. Besides the role of the kidneys in nocturia linked to arterial hypertension, chronic kidney disease is an independent predictor of nocturia through an osmotic diuresis mechanism. Some evidence suggests a close relationship between the heart (nondipping arterial hypertension), kidneys (chronic kidney disease), and nocturia/nocturnal polyuria. These complex interactions between the heart, kidneys, and bladder warrant a multidisciplinary approach in patients with nocturia.

**Patient summary:** We review the different mechanisms that lead to nocturia and nocturnal polyuria. The complex interactions between the heart, the kidneys, and the bladder warrant a multidisciplinary approach in patients with nocturia. Careful investigation of the cause of nocturia can improve its management.

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1. **Introduction**

Nocturia is the complaint whereby an individual wakes one or more times at night to void. It is a common symptom in both women and men and it is considered one of the most bothersome lower urinary tract symptoms (LUTS) [1]. Its prevalence increases with age and varies according to definitions. Nocturia involving two or more micturitions per night affects up to 60% of men and women older than 65 yr [2,3]. Nocturnal voids can be due to either real nocturia (RN), characterized by small voided volumes, or nocturnal polyuria (NP). Although different definitions of NP have been proposed, all of them assume that urine production during the night exceeds functional bladder capacity because of increased production of urine during sleep. Epidemiology suggests that the prevalence of nocturia increases with age.

RN often depends on prostate or bladder conditions such as benign prostatic enlargement obstruction, urgency with or without detrusor overactivity, reduced functional bladder capacity, and chronic urinary retention, while NP

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is often determined by systemic conditions affecting water and salt balance that lead to excessive production of urine at all times (global polyuria) or overnight (NP) [4]. Nocturia should no longer be considered just a symptom of disorders affecting the urinary system, and the diagnostic algorithm includes a number of internal medicine conditions that every urologist must be aware of [5,6].

The aim of this mini-review is to examine the role of the heart, kidneys, and bladder in the causes of nocturia.

2. Evidence acquisition

A systematic review of the literature using the Medline, Scopus, and Web of Science databases for relevant articles published up to January 2019 was performed with both MeSH and free test protocols. The MeSH search was conducted by combining the following terms: “kidney”, “heart”, “bladder” “hypertension”, “chronic kidney disease”, “coronary artery disease”, “nocturia”, “nocturnal polyuria”, “arrhythmia”, “heart failure”, and “kidney failure”. In addition, selected references from the bibliographies of the full-text manuscripts chosen were identified and added to the list. English language text was not a specific parameter, however, only English language publications were considered. The title and abstract for each article were reviewed for their appropriateness and relevance to the relationship to nocturia by two authors (A.T. and R.L) and a third author was involved (F.B.) in the case of disagreement. Real nocturia (RN) is defined as the complaint that the individual has to wake at night one or more times to void small volumes. Nocturnal polyuria (NP) is defined as urine production during the night which exceeds functional bladder capacity.

3. Evidence synthesis

3.1. The heart

NP is a common symptom in patients with heart diseases. In a systematic review, Feldstein [7] evaluated the available evidence linking RN/NP and arterial hypertension (AH) and found strong epidemiological evidence for a link. Hypertension appears to be related to NP through its effects on glomerular filtration and tubular transport; the main mechanisms involved are renal hyperfiltration and an increase in atrial natriuretic peptide (ANP). ANP is released as a result of atrial stretch due to congestive heart failure resulting from AH. Moreover, AH and the use of calcium antagonists (eg, amlopidine) may be associated with peripheral edema. The nightly reabsorption of peripheral edema increases urine volume.

Another link between AH and NP is sleep apnea. Obstructive sleep apnea is associated with obesity, elevated sympathetic nervous system activity, and AH. Abnormally low production of antidiuretic hormone (ADH) has been implicated as one of the physiological mechanisms for NP in obstructive sleep apnea. Besides a clear relationship between heart diseases and NP, the relation between cardiological drugs and RN and NP should be considered. Both calcium channel blockers and diuretics are associated with a higher risk of NP. In addition, β-blockers decrease bladder capacity and can cause nocturia if taken just before going to bed. α1-Adrenoceptor antagonists relieve nocturia in selected patients and other symptoms of bladder outflow obstruction in elderly men with prostatic hyperplasia. It is hypothesized that the therapeutic effect of α1-adrenoceptor antagonists on AH may decrease NP and explain the positive effect on nocturia observed in some patients. Lastly, nocturia has been proposed as a risk factor for AH. Compared with daytime values, blood pressure (BP) in most subjects is considerably lower during the night and attenuation of this physiological nocturnal decline is defined as nondipping AH (NDAH). Some studies suggest that an increase in nocturnal activity related to nocturia may explain a nondipping BP profile (defined as failure of the nocturnal BP to fall by at least 10% of daytime BP) [7,8]. NDAH itself is a risk factor for the development of end organ damage, including left ventricular hypertrophy, congestive heart failure, and microalbuminuria, which, as mentioned earlier, can contribute to NP, thus creating a vicious loop involving nocturia, NDAH, and NP.

3.2. The kidneys

The kidneys play a major role in patients with NP specifically related to AH, as discussed above. However, there is some evidence suggesting a direct relationship between kidney diseases and NP. NP resulting from impaired ability to concentrate urine or natriuresis makes nocturia one of the initial presenting symptoms of chronic kidney disease (CKD). In patients with CKD the prevalence of nocturia is as high as 64.0%. Interestingly, a large-scale cohort study indicated that self-reported NP is an independent risk factor for end-stage renal disease. According to Fukuda et al [9] the main mechanism causing nocturia in CKD is osmotic diuresis rather than water diuresis. It has also been suggested that nocturia reflects a high volume of fluid ingestion, which is detrimental in patients with kidney disease because high urine volume increases intratubular volume and pressure, which in turn induce fibrosis [9]. Moreover, Agarwal et al [10] found a strong association between CKD, NDAH, and NP, which opens new insights into the relationship between kidney diseases and RN/NP. Although the peer-reviewed literature clearly shows a relationship between kidney diseases, NDAH, and NP, well-designed studies to clarify the underlying mechanisms are still lacking.

3.3. The bladder

The role of the bladder in RN is mainly related to a lower functional bladder capacity (FBC) and overactive bladder (OAB) syndrome. RN caused by diminished nocturia bladder capacity (NBC) is of two general types: decreased FBC and decreased NBC. In both conditions, the nocturnal volume urinated exceeds the bladder capacity and the patient is awakened by the need to void because the bladder capacity is not sufficient [11]. The relation between RN and OAB has been investigated in several studies [12-14]. Ge et al [14] evaluated sleep disturbances and found that OAB patients
had a greater number of nighttime urinations than controls did (2.6 ± 1.1 vs 0.9 ± 0.7; p < 0.001). The odds ratio for having one or more nighttime urinations was 6.9 (95% confidence interval [CI] 1.31–36.1) in the OAB group (94.0% vs 76.7%; p = 0.023). The odds ratio for having two or more nighttime urinations was 41.9 (95% CI 10.7–164.8) in the OAB group (86.0% vs 13.3%; p < 0.001) [14]. Although these associations are well demonstrated in the literature, the exact pathophysiological mechanisms involved are still a matter of debate.

3.4. The heart, kidneys, and bladder in relation to nocturia

The above evidence clearly suggests that the heart, kidneys, and bladder are important actors in the development of RN/NP. Family physicians often underestimate the presence of RN/NP as they do not identify the symptom, which is always considered during a urological consultation [15]. When more than two nocturnal voids are identified, use of a bladder diary is recommended to differentiate RN from NP. The higher the number of nocturnal voids, the higher is the risk of NP. In cases of NP, urologists should consider a diagnostic algorithm that includes a number of systemic conditions affecting both the heart and the kidneys [16]. Although RN/NP is often first diagnosed in a urological consultation, a multidisciplinary approach is warranted and must be part of the core curriculum in urological training.

Conflicts of interest: The authors have nothing to disclose.

References


