INTRODUCTION

Nocturia is defined as waking one or more times to void during the period between going to bed with the intention of sleeping and waking with the intention of arising ***(Lee et al., 2010),*** it is a common reason for interrupted sleep in elderly adults. Nocturnal polyuria (NP) is a sub classification of nocturia characterized by nocturnal urine volume that is over 33% of the 24-h voided volume ***(Chen et al., 2016).***

There are many causes for nocturia, as with aging some people produce less anti-diuretic hormone (ADH) resulting in more production of urine at night, furthermore, the heart and circulatory system seems to be less effective at day time. This results in fluid collecting in the tissues of the body during the day, but at night heart and circulatory system work more easily and absorb this fluid into bloodstream. It is then pumped back to kidneys where it is passed out of the body as extra urine, also some medical conditions as congestive heart failure, obstructive sleep apnea, nephrotic syndrome, autonomic neuropathy, chronic kidney disease, solute or water diuresis, neurologic diseases (Parkinson's disease, Alzheimer's disease), in addition to excessive fluid intake may lead to nocturia ***(Jin and Moon, 2008).***

Managing nocturia is best based on an approach that targets the underlying causes, but changes in several empirical lifestyle factors might be effective as reducing fluid intake 6 h

before recumbency, reduce caffeine and alcohol intake, compression stockings and continuous positive airway pressure (for obstructive sleep apnea) ***(Jin and Moon, 2008).***

Desmopressin is a synthetic analogue of arginine vasopressin (AVP), but Desmopressin is More potent than AVP. Desmopressin is effective against nocturia with or without polyuria when administered at bed-time, by decreasing night-time urine production ***(Mattiasson et al., 2002).*** It works at the level of the renal collecting duct by binding to V2 receptors, which signal for the translocation of aquaporin channels. The presence of these aquaporin channels in the distal nephron causes increasing water reabsorption from the urine ***(Kataoka et al., 2015).***

Desmopressin has a level 1, grade A recommendation from the International Consultation on Incontinence and European Association of Urology for the treatment of nocturia associated with polyuria, and is currently approved for this indication in more than 80 countries outside the United States ***(Sand et al., 2013).***

Hyponatremia remains the only clinically relevant adverse effect reported with desmopressin, with the highest incidence in elderly patients and at higher dose levels and patients should be oriented by its warning symptoms that could be absent, mild or sever. Mild symptoms include headache,

decrease ability to think, poor balance and nausea. Severe symptoms include confusion, seizures and even coma ***(Weiss et al., 2013)*.**

The incidence of hyponatraemia can be reduced by using minimum effective gender-specific dosing of desmopressin. A sodium monitoring plan is proposed whereby baseline sodium must be ≥135 mEq/L (especially important in the elderly), in addition to careful medical history taking and concomitant medications ***(Juul et al., 2017)*.**

AIM OF THE WORK

The aim of this study is to determine early serum sodium changes in elderly patients with nocturia receiving Desmopressin.

Chapter 1
PATHOPHYSIOLOGY OF NOCTURIA

Nocturia is defined as the need to awaken ≥ 1 times per night to void. It is divided into two main categories: upper urinary tract and lower urinary tract dysfunction. However, nocturia has long been considered one of a range of symptoms associated with well-recognized lower urinary tract symptoms (LUTS), such as benign prostatic obstruction (BPO) and overactive bladder (OAB). This assumption is not surprising, given that BPO and OAB are generally associated with urinary frequency. However, nocturia is urinary frequency that occurs during nighttime sleep, it is not necessarily driven by a lower urinary tract dysfunction involving the bladder, prostate, or urethra; it may be driven instead by nighttime urine overproduction or nocturnal polyuria (NP), resulting from renal, cardiovascular or pulmonary factors ***(Van Kerrebroeck et al., 2002).***

Although nocturia has been shown to be one of the most bothersome LUTS and despite much emphasis placed on the need to improve patient reported outcomes in all LUTS, nocturia has not received the clinical attention that it deserves ***(Weiss et al., 2011).***

In a trial reporting the impact on nocturia of BPO and OAB medications, such as alpha-blockers and antimuscarinics,

the clinical significance of the reductions in nocturnal voids, although in some cases demonstrating statistical significance, is yet to be determined ***(Smith and Wein, 2011). Chen and Colleagues in 2007*** considered nocturia to be of minor concern and do little to dispel the myth that nocturia is a normal part of aging.

Nocturia is, however, an important condition that warrants specific clinical attention. Repeated nocturnal voiding can result in chronically disturbed sleep, which in turn negatively affects a patient's quality of life (QoL) and general health. In addition to daytime lack of vitality and the overall bother caused by waking at night to void, poor sleep can contribute to the exacerbation of existing health conditions. Furthermore, there is mounting evidence that nocturia may be associated with an increased mortality risk, via its detrimental effects on sleep and other associated comorbidities ***(Weiss, 2012).***

Prevalence:

5-15% of people who are 20–50 years old, 20-30% of people who are 50–70 years old, and 10-50% of people 70+ years old, urinate at least twice a night. Nocturia becomes more common with age. More than 50 percent of men and women over the age of 60 have been measured to have nocturia in many communities. Even more over the age of 80 are shown to experience symptoms of nocturia nightly ***(Ancoli-Israel et al., 2011).***

Nocturia symptoms also often worsen with age. Although nocturia rates are about the same for both genders, data shows that there is a higher prevalence in younger women than younger men and older men than older women ***(Park and Kim, 2013).***

Pathophysiology of nocturia:

The pathogenesis of nocturia is complex and sometimes multifactorial, involving several organ systems. Furthermore, some conditions or diseases are complicated by environmental, behavioral and pathologic factors. The mechanism responsible for nocturia includes any conditions resulting in abnormally increased urine production, decreased bladder storage capacity, or disturbed sleep pattern leading to waking at night ***(Jin and Moon, 2008).***

Looking into the mechanism of nocturia involved in different disease states gives further insight into the complex multifaceted pathophysiology. For example, although the mechanism between nocturia and HTN is not fully explained, HTN and nocturia may share similar pathophysiology with alterations in nitric oxide metabolism and resetting of the pressure natriuresis balance in the kidney leading to sodium retention and compensatory nocturnal natriuresis ***(McKeigue and Reynard, 2000).***

Nocturia is the most common LUTS. Although its prevalence is generally underestimated, nocturia is in fact an

extremely common condition, affecting both men and women of all ages. Almost 69% of men and 76% of women in the United States, United Kingdom, and Sweden, randomly selected from Internet-based panels (20,000 participants in the United States, 7500 in the United Kingdom, and 2500 in Sweden), reported ≥ 1 nocturnal voids ***(Coyne et al., 2009).***

In a review of 43 studies of the prevalence of nocturia around the world, ***Bosch and Weiss in 2010*** reported that, although nocturia is most prevalent in older people, it also affects a significant proportion of younger individuals. For instance, 4% to 18% of women in their 20s and 30s were affected by ≥ 2 voids per night, increasing to 28% to 62% for women in their 70s and 80s. Similar ranges were reported in men. The proportion of men aged 20 to 30 years reporting ≥ 2 voids per night was 2% to 17%, rising to 29% to 59% in men aged 70 to 80 years.

In European Pain in Cancer (EPIC), a population-based, cross-sectional telephone survey of 19, 165 adult men and women in five countries (Canada, Germany, Italy, Sweden, and the United Kingdom), 13% to 17% of adults aged ≥ 40 years reported ≥ 2 nocturnal voids, increasing to 20% to 21% of middle-aged men and women and 35% to 36% of adults aged ≥ 60 years. The condition, therefore, can affect up to one in five or six younger adults, as well as up to one-third of older people ***(Markland et al., 2011).***

In addition to nocturia prevalence increasing with age, it is also common in certain racial and patient populations. Non-Hispanic black men are at greater risk for nocturia even when controlling for other factors, such as education and income ***(Markland et al., 2011).***

Almost 84% of patients in an OAB study reported nocturia among their urinary symptoms, and 71% of patients with benign prostatic hyperplasia (BPH) experienced frequent nighttime voiding (ie, 2 or more episodes per night) ***(Brubaker and FitzGerald, 2007).***

Impact of nocturia on overall health and QoL:

Although nocturia is defined as waking to void ≥ 1 time, a significant impact of nocturia on patient QoL is considered to be bothersome when ≥ 2 nocturnal voids are experienced. Sleep plays a vital role in physical and mental functioning, and repeated interruptions due to nighttime voiding can reduce the quantity and quality of sleep ***(Tikkinen et al., 2010).***

For example, a cross-sectional analysis of the Sleep Heart Health study of 6342 men and women in the United States demonstrated a significant association between self-reported nocturia and objective measures of sleep disruption, such as total sleep time, sleep efficiency, proportion of REM sleep, and oxygen saturation as measured by polysomnography. Given its high prevalence, nocturia is a major cause of sleep disturbance, which is a key factor in making nocturia one of the most bothersome LUTS ***(Parthasarathy et al., 2012).***

Nocturia was associated with significant decreases in 14 of the 15 domain scores reported by men and women in the Health-Related QoL (HR-QoL) questionnaire. For every increase in nocturnal voids above 1, further reductions in HR-QoL scores were seen ***(Tikkinen et al., 2010).***

A causal relationship between nocturia and many disorders is suspected and nocturia is acknowledged to be a possible symptom of the primary illness; for example, raised blood glucose in poorly controlled type 2 diabetes can lead to polyuria, fluid accumulation in the lower extremities caused by right-sided congestive heart failure causes increased urine production upon attaining the recumbent position, and sleep apnea can increase renal sodium and water excretion due to elevated plasma atrial natriuretic peptide levels ***(Weiss et al., 2011).***

A further complication in determining causality is that many epidemiologic studies have not adjusted for factors known to contribute to nocturia, such as sleep-disordered breathing. It has been shown that sleep-disordered breathing is independently associated with increased cardiovascular risk; thus, failure to exclude this or other known causes of nocturia may lead to erroneous associations between nocturia and certain morbidities ***(Parthasarathy et al., 2012).***

A reduction in sleep quality is independently associated with indicators of poor health common to those associated with

nocturia, including disturbed glucose homeostasis, diabetes and hypertension. The direction of the cause-and-effect relationship between sleep and poor health is not always proven ***(Bliwise et al., 2009).*** The hypothesis that there may be a direct link between nocturia and mortality in an elderly population is supported by ***Lightner et al. in 2012*** who showed an association of nocturia with mortality in men aged ≥ 60 years.

The increased mortality rate associated with nocturia was likely due to its association with impaired sleep, as well as the increased risk of falls and related fractures in patients with nocturia, especially elderly patients. Poor sleep is associated with all-cause mortality and sleep parameters such as sleep efficiency have been shown to independently predict mortality ***(Nakagawa et al., 2010).***

However, a 15-year follow-up of 1114 Dutch men, aged 50 to 78 years, challenges the association between nocturia and increased risk of mortality. When age was taken into account, no association between nocturia and mortality risk existed. The multifactorial causes of nocturia, the increasing prevalence of the condition with age, and the frequent comorbidities in patients with nocturia make conclusions on the impact of mortality a challenge. Nocturia may impact health and survival because of the persistent negative effect frequent nocturnal voiding has on sleep. Regardless of whether nocturia is a

condition directly implicated in causing poor health, or whether nocturia is simply a symptom heralding the presence of another important underlying medical condition, the general finding of increased risk of significant illness associated with nocturia indicates that nocturia should be thoroughly investigated in each individual ***(van Doorn et al., 2012).***

Chapter 2

CAUSES OF NOCTURIA

The cause of nocturia in older adults is multi-factorial. Age-related changes in the urinary system along with a variety of hormonal changes (table 1) contribute to nocturia. In addition, medical conditions and medications can increase urine production or predispose to nighttime awakenings and thus increase the risk of nocturia (table 1). Psychological conditions (e.g., depression and family stress) may also contribute to nighttime awakenings ***(Weiss et al., 2011).***

Table (1): Some factors that contribute to nocturia in older adults ***(Weiss et al., 2011)***

Age-associated changes	Decreased ability to postpone urination Decreased bladder compliance Decreased functional bladder capacity Decreased maximum urinary flow rate Detrusor overactivity Increased post-void residual volume
Increased urine production at night	Increased nocturnal catecholamine levels Increased nocturnal natriuretic peptide levels Increased nocturnal sodium excretion Decreased nocturnal antidiuretic hormone levels

Table (2): Conditions and medications associated with nocturia ***(Weiss et al., 2011)***

Medical Conditions	Diabetes mellitus Heart failure Hypertension Obstructive sleep apnea Prostate enlargement Recurrent cystitis Spinal stenosis
Medications	Antihistamines Beta blockers Calcium channel blockers Cholinesterase inhibitors Diuretics taken in the evening

Nocturia is a multifactorial condition:

The pathophysiology of nocturia is complex and multifactorial, which may partly explain why the condition has not received appropriate attention as a disorder on its own. The underlying causes may be urologic or non-urologic in origin ***(Weiss et al., 2011).***

Although the causes of nocturia may differ among patients, multiple factors may underlie the cause of nocturia in

any given patient. Failure to incrementally evaluate the potential underlying factors may lead to poor clinically relevant outcomes because the major causes of nocturia may not be addressed. Therefore, it is paramount that clinicians are aware of the multiple potential contributing factors in any given patient, in order to enable optimal treatment decisions that address each issue adequately. Nevertheless, nocturnal overproduction of urine at night (20% to 33% of daily total urine volume depending on age), also known as NP, has been implicated as a significant causal factor in up to 88% of nocturia cases ***(Weiss et al., 2011).***

Nocturia is common among patients suffering from BPO or OAB, and their nocturnal urinary frequency may be an extension of their daytime symptoms because of diminished bladder storage capacity. However, the modest clinical improvement of nocturia in patients receiving BPO or OAB medications suggests that the key underlying cause of nocturia in these patients, as just mentioned, may not solely be their enlarged prostate or bladder dysfunction ***(Brubaker and FitzGerald, 2007).***

Overproduction of urine at night may result from a number of factors, such as evacuation of daytime third-space fluid sequestration with peripheral edema due to a recumbent position for sleep, excessive production of atrial natriuretic peptide due to sleep apnea or congestive heart failure, abnormalities in antidiuretic hormone arginine vasopressin