Chapter 17: Fluid Balance Disorders in the Elderly

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Disorders of fluid balance are common in the elderly and often are caused by age-related alterations in urinary tract function, which can present clinically as urinary frequency, nocturia, and incontinence. Among the factors predisposing to the development of these clinical disturbances are aging changes in the renal and hormonal systems that control water and sodium excretion along with changes in the reservoir function of the bladder[1] (Table 1). This chapter will examine the effect of aging on the systems involved in urine formation and consider how these changes interact with those of bladder function and lead to urinary frequency, nocturia, and incontinence.

In young, healthy persons there is a circadian pattern to urine production in which nighttime urine flow rate is less than daytime flow rate. In association with the normal aging process, there is an increase in nocturnal production of urine, so that nighttime urine flow rate equals or exceeds daytime production rate.[2] When of sufficient magnitude to result in nocturia, this change has been termed nocturnal polyuria syndrome.

The establishment of a circadian rhythm of urine flow takes place during childhood, generally between the ages of 2 to 5 yr. In normal children with a mean age of 7 yr, daytime rate of urine production is two to three times that of the nighttime period. Delay or failure of the circadian rhythm to develop during childhood is associated with the presence of nocturnal enuresis. In adulthood, the ratio of daytime to nighttime urine production is usually greater than 2:1, so that about 25% or less of daily urine output occurs during sleep. Typical urine production rates are approximately 70 to 80 ml/h during the waking period and 30 to 40 ml/h during sleep. This circadian pattern seems to be linked to the day-night sleep pattern. The circadian pattern of urine flow is paralleled by similar rhythms of renal plasma flow and GFR. The circadian pattern is maintained in healthy persons until around age 60 yr when a shift to a greater proportion of urine production to the nighttime period becomes evident. With further increase in age, there is often reduction in the ratio of day to night urine flow to the point that nighttime flow rates become equal to or exceed daytime rates. Despite the change in circadian pattern of urine excretion, total urine production per 24 h is not affected.[3]

ARGININE VASOPRESSIN SECRETION

Arginine vasopressin [AVP; antidiuretic hormone (ADH)] is the major hormone responsible for the regulation of urine formation. The magnocellular supraoptic and paraventricular nuclei of the hypothalamus where AVP is synthesized do not seem to undergo age-related degenerative changes with either morphologic features of cell destruction or decline in cell hormone synthetic ability or hormone content.

There is some controversy regarding the influence of normal aging on daytime blood AVP levels. A number of studies have indicated that, under basal conditions, daytime plasma AVP concentration is not affected by increasing age. In contrast, several other studies have reported increased basal plasma AVP levels in healthy elderly persons. Further adding to controversy are reports that healthy elderly subjects have daytime plasma AVP concentrations that are significantly lower than in young subjects.

In healthy adults, there is a diurnal release of AVP into the circulation with peak blood concentration occurring during the hours of sleep. This rhythm seems to be linked to the wake-sleep cycle

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Table 1. Physiologic changes of aging associated with increased urine production

Age-associated impaired renal concentrating capacity
Resistance to AVP action, *i.e.*, "acquired partial nephrogenic diabetes insipidus"
Impaired sodium conservation
Decreased nocturnal AVP secretion
Decreased renin-angiotensin-aldosterone secretion
Increased atrial natriuretic hormone secretion

rather than to time of day. The circadian rhythm becomes established during childhood and delay in its maturation is often associated with enuresis. With advanced age, there seems to be blunting of the nocturnal phase of AVP secretion so that daytime and nighttime blood levels of the hormone are similar.[4,5]

In contrast, elderly persons may have greater response of AVP secretion to several stimuli than younger persons. The plasma AVP response to intravenous hypertonic saline infusion in healthy elder subjects (age 54 to 92 yr) is almost double that of the younger subjects, suggesting that aging results in increased osmoreceptor sensitivity. Studies using water deprivation, intravenous metoclopramide, or cigarette smoking as stimuli for AVP secretion have also shown a similar age-related enhancement of response. In contrast, the stimulation of AVP release by BP reduction or upright posture seen in young persons did not occur in elderly subjects, indicating an age-related impairment of volume/pressure mediated AVP release most likely related to impaired baroreceptor function.

RENAL WATER LOSS

In association with normal aging, there is a decline in renal concentrating capacity. After 24 h of dehydration, there is a progressive decline in maximal urine osmolality with increasing age. This effect of aging persists even after correction for the age-related decline in GFR. The decline in renal concentrating ability of the aging kidney is not caused by an inadequate response of AVP to the stimulus of water deprivation but rather to impaired renal tubular response to AVP. Thus, aging can be considered to lead to the development of an acquired form of partial nephrogenic diabetes insipidus. Age-associated increased excretion of urea can also contribute to increased urine excretion through its osmotic effect. Under conditions of adequate intake of fluid, these changes may result in no apparent clinical consequence other than mild increase in urine flow rate, but the elderly person who has restricted fluid intake may be unable to adequately reduce urine formation and therefore be at increased risk of dehydration.

RENAL SODIUM LOSS

Normal aging is associated with impaired ability of the kidney to retain sodium. In very old persons, sodium reabsorption in the thick ascending loop of Henle is impaired and can contribute to both sodium loss and to impaired tonicity in the renal medulla. After the administration of an acute water load with consequent expansion of intravascular volume, there is an exaggerated natriuresis in elderly individuals compared with younger subjects. An excess of sodium excretion with increasing age has been described in patients with mild hypertension. The ability of the aged kidney to conserve sodium in response to salt restriction is sluggish. Restriction of dietary sodium intake to 10 mEq/d resulted in a half-life for reduction of urinary sodium excretion of 17.6 h in young individuals in contrast to 30.9 h in old subjects. The tendency to sodium wasting in elderly persons can lead to natriuresis with an accompanying obligatory osmotic diuresis, especially when individuals are in the recumbent position.

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The ability of the kidney to conserve sodium is partly dependent on the actions of the renin-angiotensin-aldosterone system, a system affected by the normal aging process.[6,7] Healthy older individuals (age 62 to 70 yr) who consume a normal amount of dietary sodium have lower levels of both plasma renin activity and aldosterone in the supine position than young healthy persons age 20 to 30 yr. After the combined stimuli of low dietary sodium intake and upright posture, plasma renin activity and aldosterone concentration increase in both age groups, but the mean values achieved are significantly lower in the elderly persons group. Decreased conversion of inactive to active renin may be at least partially responsible for the reduction in active renin concentration in elderly persons. The age-related decrease in plasma renin results in decreased aldosterone production by the adrenal gland. Age itself does not affect the ability of the adrenal gland to synthesize and secrete aldosterone because stimulation of the adrenal by corticotropin infusion results in similar increases of both plasma cortisol and aldosterone in young and elderly subjects. It is likely that the age-related reduction in aldosterone concentration is one of the factors associated with impaired renal sodium conserving ability in elderly persons. There does not seem to be an effect of age on renal tubular responsiveness to aldosterone.

ATRIAL NATRIURETIC HORMONE

ANH may be a significant factor in mediating the altered renal sodium handling of the elderly. Through its action on the kidney, it produces natriuresis and obligatory diuresis. A number of studies have shown that ANH concentration in the blood is increased with aging. Mean basal plasma ANH levels were fivefold higher in elderly male nursing home residents than in young normal men.

In addition, the intravenous infusion of normal saline re-

sulted in an exaggerated rise in plasma ANH concentration in the elderly persons group. Several other studies involving healthy elderly persons have also established that basal plasma ANH concentration is increased and that stimuli that can increase intracardiac pressure result in a greater rise of plasma ANH in elderly persons than in the young. There is evidence that the renal response to ANH may also be greater in elderly persons. The natriuretic response to a bolus injection of ANH has been observed to be larger in older persons with a mean age of 52 yr than in younger persons with a mean age of 26 yr.

ANH has been shown to interact with the renin-angiotensin-aldosterone system. High levels of ANH suppress renal renin secretion, plasma renin activity, plasma angiotensin II, and, as a consequence, plasma aldosterone. Even minimal increases of ANH within the physiologic range produced by slow-rate intravenous infusion of ANH are capable of inhibiting angiotensin II-induced aldosterone secretion, providing support for the functional impact of the increased ANH levels in elderly persons. ANH can also suppress plasma aldosterone by a direct effect on aldosterone secretion. Thus, ANH may be an important contributor to age-related impaired renal sodium conserving ability, and concomitant water loss, both through its direct natriuretic effect and through ANH-induced suppression of aldosterone secretion.[8]

The above studies clearly establish that normal aging is accompanied by increased urine excretion during the nighttime period of sleep. There are multiple physiologic changes in renal water and sodium conserving mechanisms and in the hormonal systems governing water and sodium regulation. The effect of these changes is to alter the diurnal rhythm of urine excretion in the direction of nighttime diuresis (Table 2).

AGING EFFECTS ON BLADDER RESERVOIR FUNCTION

In healthy adults, 24-h urine production is usually in the range of 1000 to 1500 ml and bladder capacity generally ranges from approximately 400 to 750 ml. This is associated with a daytime voiding frequency of four to five times in men and five to six times in women and with rare voiding during normal periods of sleep. There is a suggestion that voiding frequency increases with age, especially in men. With advancing age, there is a progressive increase in the prevalence of urgency, most commonly caused by detrusor instability. The prevalence of urgency increases to 40 to 49% in men from the fifth to seventh decades and to 40 to 50% in women in their fifth decade and beyond. In institutionalized elderly persons with incontinence, 72% were found to have detrusor instability. The clinical consequence of detrusor instability is decline in functional bladder volume so that small urine volumes result the sensation of full bladder and the initiation of bladder contractions leading to an increase in the frequency of voiding during the day and at night (Table 3).

Table 2. Typical parameters related to circadian water excretion in healthy young and elderly adults*

	Young		Elderly	
	Day	Night	Day	Night
Urine volume (ml/h)	75	35	50	70
Urine osmolality (mosm/kg)	700	830	510	450
Plasma AVP (pg/ml)	1.1	2.0	1.9	1.3
Plasma ANH (pg/ml)	19	17	40	55

*Data show typical values based on literature and/or author's experience.

NOCTURNAL POLYURIA SYNDROME

The constellation of increased nocturnal urine production and consequent nocturia with its associated effects on disruption of sleep has been termed the nocturnal polyuria syndrome.[3,9,10] Several definitions have been used in characterizing individuals as having nocturnal polyuria: (1) urine output during sleep $\geq$33% of total 24-h volume; (2) nighttime urine flow rate $\geq$0.9 ml/min; and (3) 7:00 p.m. to 7:00 a.m. urine volume $\geq$50% of total 24-h volume. A number of clinical states have been associated with the development of nocturnal polyuria (Table 4).

In persons with nocturnal polyuria, there is an absence of diurnal change in plasma AVP concentration. Both urinary frequency and hourly urine volume are greater at night in older persons with nocturnal polyuria syndrome and, in these individuals, functional bladder capacity is lower at night with an approximate volume of 200 ml. Patients with nocturia have significantly lower urine osmolality at night. Both plasma AVP and angiotensin II are lower at night in patients with nocturnal polyuria, and plasma ANP levels have been found to be higher.[4,5] Both the nocturnal decrease in AVP and the nocturnal rise in ANP seem to be responsible for the high nighttime urine flow and resultant nocturia. In association with reduction in functional bladder volume, the clinical consequence is nocturia.

Nocturnal Polyuria in Multiple System Atrophy

Multiple system atrophy (MSA) is a central nervous system degenerative disease that most commonly occurs in older persons. It affects many areas of the central nervous system and has central autonomic insufficiency or Shy-Drager syndrome as one its components. Patients with central autonomic insufficiency have been observed to excrete large amounts of urine when recumbent at night, and this noc-

Table 3. Association between nocturnal urine flow rate, bladder volume, and nocturnal urinary frequency in healthy young and elderly adults*

	Young	Elderly
Nighttime urine flow rate (ml/h)	35	70
Time in bed (h)	8	8
Nighttime urine production (ml)	280	560
Bladder capacity (ml)	400	200
Number of voids during sleep period	0	2

*Data show typical values based on literature and/or author's experience.

Table 4. Clinical states associated with nocturnal polyuria syndrome

Nocturnal polyuria syndrome
Primary enuresis in children
Normal aging
Multiple system atrophy
Alzheimer's disease
Spinal cord injury
Other causes of increased nocturnal urine production
Edematous states
CHF
Renal disease
Hepatic disease
Venous insufficiency
Osmotic diuresis
Diabetes mellitus
Diuretics
Impaired renal concentrating ability
Renal disease
Hypokalemia
Hypercalcemia
Increased fluid intake
Iatrogenic
Primary polydipsia

turnal dieresis is associated with marked decrease in nocturnal AVP production with a resultant diabetes insipidus-like nocturnal diuresis. Treatment of MSA patients who have nocturnal polyuria with the AVP analogs DDAVP (desmopressin) or lysine vasopressin has resulted in reduction of nocturnal polyuria and improvement in the orthostatic hypotension that is part of the syndrome and worsened by the polyuria-caused intravascular volume depletion.

Nocturnal Polyuria in Alzheimer's Disease

The synthesis of AVP by hypothalamic neurons is not affected in patients with Alzheimer's, but AVP release into the circulation is impaired so that AVP concentration in the blood has been reported to be lower in patients with Alzheimer's disease than in comparably aged persons with normal cognitive function. In patients with Alzheimer's disease, there is loss of nocturnal AVP secretion and an accompanying reversal of day-night urine production and nocturnal polyuria. Both the decrease in daytime AVP release and the loss of nocturnal secretion put patients with Alzheimer's disease at increased risk for fluid loss and dehydration. Clinically, this can be expressed by the high prevalence of nocturia and both daytime and nighttime urinary incontinence in patients with Alzheimer's disease. Detrusor instability is commonly present in patients with Alzheimer's disease. The combination of high nighttime urine production, decreased functional bladder volume, and cognitive impairment can readily explain why >80% of institutionalized patients with Alzheimer's disease have urinary incontinence. When there is impaired mobility as well, the underlying factors are likely to result in near 100% presence of incontinence (Table 5).

Table 5. Factors predisposing patients with Alzheimer's disease to nocturia and urinary incontinence

Decreased urine concentrating ability
Decreased plasma AVP and loss of circadian rhythm
Increased nocturnal urine flow rate
Decreased functional bladder volume (detrusor instability)
Diminished perception of bladder fullness
Diminished appropriate toileting behavior
Diminished mobility

Other clinical conditions that may be associated with increased nocturnal urine production include edematous states such as congestive heart failure, renal and hepatic disease, and peripheral venous insufficiency, where edema fluid may be mobilized when individuals are in the recumbent position. Osmotic diuresis, as occurs in patients with poorly controlled diabetes mellitus and after administration of diuretic drugs, can also lead to increased nocturnal urine flow. Although uncommon in elderly persons, high fluid intake states, as may be seen in patients with primary polydipsia or in individuals who ingest large fluid volumes in the belief that doing so is beneficial, can cause nocturnal polyuria.

THERAPY OF NOCTURNAL POLYURIA SYNDROME

Hormonal

The demonstration of reduced daytime and/or nocturnal AVP secretion in patients with nocturnal polyuria suggests that hormone replacement therapy with AVP or its potent antidiuretic analogs may be beneficial in reversing the syndrome.[11–13] Short-term treatment with 20 μg of intranasal DDAVP for 2 wk results in a 25 to 40% reduction of nocturnally voided urine with a corresponding reduction in nocturnal frequency. Prolonged treatment for 2 mo with 40 μg of DDAVP daily has shown a sustained response and a decrease in nocturnal urgency and incontinence.

Intranasal doses of DDAVP ranging from 10 to 40 μg daily were capable of producing a 10 to 50% reduction in nocturnal urine volume in Alzheimer's disease patients with nocturnal incontinence. Long-term treatment of these patients with 10 μg DDAVP daily has been observed to result in restoration of nighttime continence in some individuals (Table 6).

The use of DDAVP in the treatment of the elderly patient with nocturia and nocturnal polyuria may be associated with adverse effects because of water retention, especially when DDAVP is administered in the intranasal form, with as many as 20% of treated patients developing hyponatremia. Thus, use of DDAVP for treatment of nocturnal polyuria should be limited to the oral preparation. In addition, DDAVP effect may be limited by age or disease-associated impairment of renal concentrating response.

Table 6. Treatment of nocturnal polyuria syndrome

Hormone replacement: DDAVP (desmopressin)
Intranasal: 20–40 μg
Oral: 0.1–0.4 mg
Anticholinergic agents (detrusor antispasmodics)
Oxybutynin: 2.5–5 mg, bid to qid
Oxybutynin xl: 5–30 mg once daily
Tolteradine: 2–4 mg once daily
Solifenacin: 5–10 mg once daily
Darifenacin: 7.5–15 mg once daily
Trospium: 20 mg, bid
Imipramine: 1 mg/kg body weight orally at 8:00 p.m.

CONCLUSIONS

Aging is associated with changes in the renal and hormonal systems involved in the conservation of water and sodium. As a consequence, there is increase in nocturnal urine production. Concurrent age-related changes occur in the reservoir function of the bladder. The combination of increased urine production at night and decrease in functional bladder volume results in the development of nocturnal urinary frequency and predisposes to the development of urinary incontinence. Diminished AVP secretion in patients with Alzheimer's disease puts this population at even greater risk for nocturia and incontinence and the risk is further magnified by diminished perception of bladder fullness and/or impaired mobility. The availability of easily administered hormone replacement in the form of intranasal or oral DDAVP opens the possibility that for some patients there may be an effective intervention available to reduce nocturia and urinary incontinence and the clinical consequences associated with these disorders.

TAKE HOME POINTS

- Renal and hormonal changes of normal aging can result in increased nocturnal urine production in healthy elderly persons
- Functional bladder volume is often decreased in elderly persons
- Increased nocturnal urine production and decreased functional bladder volume predispose to nocturia and urinary incontinence
- Decreased nocturnal AVP production puts patients with Alzheimer's disease at high risk for nocturia and incontinence
- DDAVP may be an effective intervention in management of nocturia and incontinence in some elderly persons

DISCLOSURES

None.

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REVIEW QUESTIONS: FLUID BALANCE DISORDERS IN THE ELDERLY

1. All of the following are normal changes of aging that can lead to increased urine production except which one:
   a. Acquired resistance to the action of antidiuretic hormone
   b. Increased atrial natriuretic hormone secretion
   c. Increased nocturnal antidiuretic hormone secretion
   d. Impaired renal sodium conservation
   e. Decreased renin-angiotensin-aldosterone secretion

2. A 73-yr-old male gives a history of nocturia twice nightly for the past 3 yr. Your initial evaluation should include all of the following except which one:
   a. Digital rectal examination
   b. Asking the patient to complete and bring in a 3-d voiding diary
   c. Taking a careful history of all prescription and nonprescription medications taken
   d. Initial laboratory studies to include serum electrolytes and calcium, first voided morning urine specimen for osmolality
   e. Referral to a urologist for possible cystoscopy

3. An 83-yr-old woman with dementia attributed to Alzheimer's disease is seen for a history of worsening urinary incontinence. All of the following findings are likely to be present except which one:
   a. Urine volume from 7:00 p.m. to 7:00 a.m. is greater than urine volume from 7:00 a.m. to 7:00 p.m.
   b. Maximum bladder capacity is likely to be $>$500 ml
   c. Plasma level of atrial natriuretic hormone (ANH) will be higher than the level in normal persons in the 25 to 50 yr age range
   d. Urine osmolality in a first voided morning urine specimen is likely to be $<$700 mOsm/kg
   e. A risk of a therapeutic trial with DDAVP is the development of hyponatremia