Electrolytes in the Aging

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Abstract

The elderly population in the United States continues to grow and is expected to double by 2050. With aging there are degenerative changes in many organs and the kidney is no exception. After age forty there is an increase in cortical glomerulosclerosis and a decline in both glomerular filtration rate and renal plasma flow. These changes may be associated with an inability to excrete a concentrated or a dilute urine, ammonium, sodium, or potassium. Hypernatremia and hyponatremia are the most common electrolyte abnormalities found in the elderly and both are associated with a high mortality. Under normal conditions the elderly are able to maintain water and electrolyte balance but this may be jeopardized by an illness, a decline in cognitive ability, and with certain medications. Therefore, it is important to be aware of the potential electrolyte abnormalities in the elderly that can arise under these various conditions in order to prevent adverse outcomes.

Keywords

hypernatremia; elderly; hyponatremia; aquaporins; urea transporter; potassium; acidosis

Introduction

The elderly population has been growing rapidly over the past few decades, with an expected doubling in the United States from 38 to 81 million by 2050 (1,2). This rise is a result of advancements in medical care and the aging of the "baby boomers", those born between 1945–1964. This growth parallels the increase in the prevalence of chronic kidney disease (CKD), which is associated with a rise in diabetes mellitus, and hypertension (2,3). There are more than 20 million persons with CKD stages I through V, of which 8 million have CKD stages III, IV, and V (3). CKD stages III, IV, and V are associated with various metabolic and electrolyte abnormalities that result from the decline in kidney function. While these changes

are expected to occur with advancing kidney disease, unexpected electrolyte abnormalities may occur in the elderly without obvious kidney disease as a result of structural and functional changes associated with aging, called the "senescent kidney".

The kidney is one of the major organs in which specific structural and functional phenotypic changes occur with aging (4). Glomerular filtration rate (GFR) and renal plasma flow (RPF) decline in elderly persons compared to young adults (5–8). In cross-sectional studies, creatinine clearance falls by 0.87 cc/min/year beginning at 40 years of age (9). Interestingly, this does not hold true for all. In the Baltimore Longitudinal Study of Aging, one third of the subjects experience no decline in their renal function with age (9).

The histological changes associated with senescence have been gathered from medical examiner reports, renal transplant donors, nephrectomies, and animal studies (6, 7, 10, and 11). Structurally, the weight of the kidney declines from 400 grams at 40 years of age to 300 grams by the ninth decade, and decreases in size from 10–30% by 80 years of age (6,7,12). This decrease in size and weight is due to glomerulosclerosis in the superficial cortex of the kidney. This cortical glomerulosclerosis is less than 5% by age 40 years but increases to 10–30% by 80 years of age; the medulla is spared (7,12). Other histological findings include interstitial fibrosis with monocyte infiltration, tubular atrophy, and hyalinosis of the arterioles (7,12).

These structural changes have an impact on the functional changes noted in the aging kidney. GFR, RPF (5,13), diluting and concentrating capacity (14–17), secretion of potassium (18), and ability to excrete an acid load decline in the elderly as compared to young adults (19–20). Under normal conditions the elderly are able to maintain electrolyte balance (13). However, under stressful conditions, this ability to maintain homeostasis may be lost, making them more susceptible to hyponatremia, hypernatremia, volume depletion, volume overload, hyperkalemia, and metabolic acidosis. This article will focus mainly on plasma sodium for a few reasons: 1) it is the most common electrolyte disturbance found in the elderly; 2) it is associated with high morbidity and mortality; and 3) there is a greater understanding of water disorders than other electrolyte abnormalities.

Water Balance

In Elderly Population

The most common electrolyte abnormalities in elderly patients are the dysnatremias, and age has been found to be an independent risk factor for developing both hyponatremia and hypernatremia (21). With aging, muscle mass is replaced by fat, total body water is decreased, and intracellular volume is changed; all of these factors play a role in the increased prevalence of hypernatremia and hyponatremia (22–24). Eleven percent of the geriatric ambulatory community was found to be hyponatremic (24–25) while the prevalence of hyponatremia among hospitalized geriatric patients was 5.3% (25). Hypernatremia was found in 1% of patients greater than 60 years old admitted to the hospital (26). The prevalence of hyponatremia in many studies varies depending on the population (nursing home, community dwelling, or hospital) and depends on the definition of hyponatremia and ranges from 2.5% to as high as 50% (21,25,27–28).

At the time of admission, the hypernatremic patients were more likely to be >80 years old, female, and from a nursing home (26). An underlying infection was commonly identified as a cause (29). Dementia appears to be a common denominator for hypernatremia in hospitalized patients (33). The causes of hypernatremia may differ depending on the time of hospitalization. Urinary concentrating ability at the time of admission has been shown to be intact and suggests that increases in insensible losses and hypodypsia are early causes of hypernatremia. Very commonly, an elderly woman may be admitted from the nursing home with a past medical

history of a stroke that is now complicated by a superimposed urinary tract infection and an elevated serum sodium. The causes for her hypernatremia may be multifactorial, including: 1) an inability to get to a water source; 2) an increase in insensible loss of water from fever; 3) an inability to retain free water as a result of a decline in urinary concentrating capacity; and 4) a decrease in thirst. All of these are potential contributing factors in the development of hypernatremia.

During a hospitalization there is a decrease in the ability to concentrate the urine that often stems from medications that interfere with urinary concentrating ability. This is compounded by the patient's inability to independently get to a water source (26). In the inpatient and nursing home settings, the causes of hyponatremia stem from iatrogenic causes or from non-osmotic release of ADH in 97% of patients (27).

The known causes of the dysnatremias are numerous and are related to cognitive state, inability to concentrate or dilute the urine, medications, post-operative complications, and acute illnesses (28–41). Elderly persons are prescribed a plethora of medications that are known to be responsible for their hyponatremia and hypernatremia (Table 1). The thiazides and serotonin reuptake inhibitors are commonly prescribed medications in elderly patients and have been shown to cause hyponatremia to a much greater extent in the elderly than in other age groups (33,37). A very common scenario is an elderly patient who is prescribed hydrochlorothiazide for hypertension and later develops a low serum sodium. If the discontinuation of the thiazide results in the correction of the hyponatremia, this suggests that the thiazide is the etiology of the patient's hyponatremia. Under these circumstances, the hyponatremia is a result of the maintenance of the medullary osmolality (as opposed to loop diuretics), an increase in ADH secretion in response to a decrease in volume, and a decrease in flow to the distal tubules. The drugs listed in Table 1 and the probable mechanisms by which they cause these water disorders are important to know since both hyponatremia and hypernatremia may be avoidable as well as the corresponding high mortality and morbidity associated with them.

Mortality rates associated with hypernatremia are greater than 40% (26,29,30) and are commonly related to the underlying disease processes (26,29). They are seven times that of age matched controls and unrelated to the severity of the hypernatremia (26). In hyponatremic elderly patients, the mortality rate is twice that of those without hyponatremia (42), and even cases with only mild hyponatremia have been identified as an independent risk factor for death and myocardial infarction (43).

The inability to maximally concentrate the urine in elderly individuals has been well known for at least 50 years (44). In 1972, Dontas examined the mechanism responsible for the tubular dysfunction commonly found in the elderly population. The relative decrease in proximal tubular function correlated with the lower GFR seen with aging, but distal tubular function declined more rapidly than GFR (44). This is important because the final concentration of the urine is determined in the distal tubule. In the hydropenic state, the elderly could not concentrate the urine to the same degree as a younger cohort, 1089 ± 17 versus 808 ± 46 mOsm/kg H_2O ($p < 0.001$), nor could they excrete a maximally dilute urine following a water load, with a free water clearance of 19 ± 1 versus 11 ± 1 ml/min ($P < 0.001$). However, the inability to dilute the urine was less of a factor than the attenuation of urine concentrating ability. The impairment of the urine concentrating ability in the elderly was noted to result from a defect in the concentrating gradient in the medullary region with loss of the osmotic gradient between the urine and serum (44).

Both a decrease in urinary concentrating ability and thirst contribute to the dehydration commonly found among the elderly. Originally the inability to concentrate the urine was thought to be related to a decrease in production or secretion of ADH but both human and

animal studies showed that ADH secretion and responses to changes in serum osmolality by either tonic load or water deprivation were appropriate. If anything, ADH secretion was supersensitive in responding to changes in tonicity (15,44–49). Although serum levels of ADH are not significantly different from younger adults, loss of the nocturnal variation in ADH levels contributes to the high prevalence of nocturia among the elderly (24,45).

When the responses of healthy elderly individuals to an infusion of 5% hypertonic saline were compared to young adults, no differences in blood pressure or serum osmolality were noted at baseline among the two groups (45). The ADH at baseline was higher in the younger cohort but increased in both groups in response to hypertonic saline; however, serum osmolality and ADH rose to higher levels in the elderly. After cessation of the hypertonic solution, the time for the serum sodium to return to normal values took longer in the elderly group than in the younger population group, 9.5 hours versus 2 hours (p < 0.005), and it took slightly longer for the serum osmolality to return to baseline, 10–12 versus 4.5 hours (p < 0.005) (45). Although both groups began drinking at the same time, the urge to drink was blunted in the elderly group as they ingested 50% less fluid than the younger group. Of those patients who developed hypernatremia in a hospital setting, 86% were unable to get to a water source, further emphasizing the importance of thirst protecting against hypernatremia (29).

The decrease in solute intake from sources such as protein in the elderly may contribute to the decreased medullary concentrating ability. Urea, which is generated from the breakdown of protein, contributes heavily to the medullary tonicity (15,50). Interestingly, urea is more readily excreted in the elderly than in the younger adults. This may be due to an increase in cortisol secretion which results in less urea being reabsorbed and results in a lower medullary tonicity (15,51).

The decrease in GFR that occurs with aging reflects a decline in the number of functioning glomeruli with a corresponding decline in the number of functioning tubules. This results in the inability to dilute the urine and an increased prevalence of hyponatremia (24,28,52–53). When a water load was given to healthy elderly volunteers, they demonstrate an inability to appropriately dilute urine below 115 mOsm/kg H_2O, while healthy younger volunteers could dilute their urine below 100 mOsm/kg H_2O (44). Moreover, elderly persons, who were asked to ingest a water load, showed a decrease in electrolyte free water excretion at 2 hours compared to the younger group: 41 cc $\pm$ 2% versus 101 cc $\pm$ 4%, respectively (47). Although the peak water diuresis and peak free water clearance were lower in the older group, there was no difference between the elderly and the younger group when adjustments were made for the reduction in GFR. In this study there was no difference in the ADH level found between the age groups, suggesting that the decrease in water excretion may be related to the decrease in kidney function rather than related to an inappropriate ADH response.

Hypotonic hyponatremia can be grouped by volume status (31,53–54): either hypovolemic, euvolemic, or hypervolemic. One study found that elderly patients diagnosed with the Syndrome of Inappropriate Anti-Diuresis were actually in a low volume state. These individuals responded to mineralcorticoid rather than to fluid restriction. Institution of the latter could have worsened the clinical outcome (54).

There have been numerous studies performed on aging rodents in which cellular and molecular changes were observed that account for concentrating defects in elderly rodents, and may also help explain similar changes that occur in man. As a segway into this discussion, we will first discuss the normal physiology in the maintenance of water balance. After that we will review the changes in the physiology that result in aging as found in elderly rodents and extrapolate these findings to elderly humans.

Water Balance

Under normal conditions, water balance depends on the successful interaction of three different sites: the hypothalamus, the thirst center, and the kidney. These interact with one another to maintain plasma osmolality (49). The osmoreceptors sense a small change in the plasma tonicity that results in either ADH release or inhibition (55–57). The hypothalamus, which is located in the 3rd ventricle, is in close proximity to these osmoreceptors and the thirst center (58–59), and is responsible for the synthesis of ADH (also called vasopressin, AVP). Vasopressin is a nonapeptide produced by the periventricular and supraoptic nuclei located within the hypothalamus. Vasopressin transverses the infundibulum and is stored with neurophysin II and glycoprotein within the posterior pituitary, ready to be released into the circulation and exert a direct effect on the kidney tubules (55–57).

In addition, ADH can be released non-osmotically in response to hypovolemia, pain, nausea, or medications (31,57). Hypovolemia, true volume depletion, or a decrease in the effective blood volume stimulate the baroreceptors located in the carotid sinus, aortic arch, atrium, and pulmonary veins, and cause release of ADH by way of the medullary tract to the hypothalamus (57–59). A decrease in 10% of the blood volume results in a release of ADH in an exponential manner (57). Healthy elderly persons are often mildly hypovolemic (57). With a decrease in total body water (22), they are at high risk for hypernatremia under certain circumstances. On the other hand, an elderly patient with immobility syndrome (IS), which is characterized by an inability to perform daily tasks because of motor deterioration, experiences physiological changes such as orthostatic hypotension, low cardiac output, muscle rigidity, and have been associated with an increase in total body water and lower serum sodium (60). Although Musso et al. (60) found a correlation between the serum osmolality and ADH in healthy elderly individuals, they found none in IS patients.

The concentrating capacity in the kidney is a complex system and dependent on many variables including maintenance of renal blood flow, GFR, solute load, presence of vasopressin, functionality of vasopressin receptors, urea transporters, sodium transporters, and water channels (aquaporins) (Fig 1). In order to concentrate the urine, the medullary countercurrent system must be intact (61).

Thirteen aquaporins (AQP) have been identified. The majority are located within the kidney: AQP1, AQP2, AQP3, and AQP4 have well establishes roles (61). AQP1 is a constitutive vasopressin-independent water channel located on the apical and basolateral membranes in the proximal convoluting tubules (PCT), thin descending limb of the loop of Henle (tDL), and endothelium of the descending vasa recta, and is responsible for water transport across these membranes (62–63). The PCT is responsible for reabsorption of 60% of the glomerular ultrafiltrate. The tDL is permeable to water only via AQP1 and plays a major role in the countercurrent multiplier as shown in the dehydrated state of AQP1 knockout mice (63). Under normal conditions, the knockout mice are phenotypically normal but in a water deprived state they cannot maximally concentrate their urine and become dehydrated (63). Similarly an AQP1 mutation (Colton blood group mutation) has been discovered in humans; they are phenotypically normal in a non-stressful environment but have a defect in concentrating ability when stressed (58). AQP2, AQP3, and AQP4 are located in the collecting tubules. AQP2 is located in the sub-apical cytoplasm and the apical membrane; it is vasopressin–dependent. AQP3 and AQP4 are located on the basolateral membrane and are both constitutively active (62,65–68). AQP3 has been shown to have increased expression in the presence of ADH and greater density in the cortical region (65). These aquaporins permit water to enter previously impermeable cells; a concentrated urine results (15,62,65).

ADH binds to the V$_2$-vasopressin receptor on the basolateral membrane in the collecting tubule. These receptors are linked to adenylyl cyclase via a G protein, Gs (65,67). As a consequence,

intracellular cAMP levels rise. In turn, cAMP activates protein kinase A (69). This is followed by phosphorylation of serines 256, 261, 264, and 269 in the COOH terminus, which are important in AQP2 channel trafficking and insertion into the apical membrane by exocytosis (70).

Urea plays an important role in the countercurrent system and in the formation of a concentrated urine. The renal urea transporters are found on two different genes, SLC14A2 and SLC14A1 (see reviews 71,72). The SLC14A2 gene produces various isoforms including UT-A1, UT-A2, and UT-A3 in response to different promoter sites and alternative splicing (72). The SLC14A1 gene produces UT-B, which is located both in red cells and endothelial cells of the descending vasa recta (15,72). Urea is transported by various urea transporters located in the inner and outer medulla. These urea transporters play a specific role in maintaining the high tonicity in the corticopapillary gradient (15). UT-A1 and UT-A3 are located in the inner medullary collecting ducts, UT-A2 is located throughout the tDL, and UT-B is located in the vasa recta in the outer medulla (15,72). UT-A1 and UT-A3 are ADH-dependent transporters resulting in facilitative urea reabsorption into the interstitium with recycling of the urea by the UT-A2 transporters in the descending limb of the loop of Henle in the outer medulla (15,72).

The thick and the thin ascending loops of Henle are responsible for solute contribution to the countercurrent system (15,72–76). The thin ascending limb has been found to passively reabsorb NaCl in greater quantities than urea is reabsorbed in the inner medulla (15,74), while the NKCC2/BSC1 bumetanide sensitive Na-K-2Cl cotransporter located in the thick ascending limb of Henle actively reabsorbs Na and Cl and is regulated by vasopressin (74–76).

Thirst is important in maintaining plasma osmolality (15,32,45,52). The various known water disorders can be corrected with an intact thirst center, which is located adjacent to the osmoreceptors in hypothalamus. In the elderly, a decrease in thirst has been shown to contribute to a hyperosmotic state that is further exacerbated by the decrease concentrating capacity that occurs with aging (41,45).

Water Balance in Aging Animal Studies

A decrease in the abundances of aquaporin and urea transporter proteins has been observed with aging in the kidney of animals. This may account for an inability to concentrate and dilute the urine. In animal (77–80) and human studies (45,47,49), the ADH levels have been shown not to differ greatly from younger cohorts suggesting that the defect is related downstream, beyond the hypothalamus.

Concentrating Capacity in Rodents—There are many different sites in the nephron which are responsible for the diminished concentrating capacity that occurs with aging (Fig 2). These include the collecting tubules, the descending limb of the loop of Henle, the medullary thick ascending limb, and the descending vasa recta. Both older rats and elderly patients show an increase in polyuria, a decrease in urine osmolality, and an inability to concentrate the urine when compared with younger age groups (45,80,82–83). The collecting tubule, which contains the V_2-vasopressin receptor on the basolateral membrane, is responsible for the final concentration of the urine. Although 30 month old rats showed a 30% decrease in the number of binding sites for vasopressin in the basolateral membrane, intracellular cAMP levels were adequate, suggesting that a downstream defect accounted for the decrease in concentrating capacity (81). In addition, there was decreased expression of AQP2 (80%) and AQP3 (50%) within the inner medulla, but there was no change in either AQP1 or AQP4 expression (81). Similar findings were noted in the F344BN rat. There was a 30% decrease in the expression of AQP2 in the inner medulla of 24 month old rats compared to 3 month old rats (82). Immunohistochemical studies revealed a lack of AQP2 in the sub-apical and apical regions (51,81–82). Under conditions of water deprivation (76) or chronic infusion of dDAVP (81), a

V_2 selective agonist, AQP2 and AQP3 expression were increased and AQP2 relocated to the apical and sub-apical membrane, as expected (51,82). However, urine osmolality did not increase as much, and urine volume did not decrease as much, in the older rats as compared to younger rats (51,82). Besides the decrease in AQP2 expression, there was impairment of the phosphorylation of AQP2. This may interfere with the trafficking and exocytosis of AQP2 into the apical membrane of principal cells in the collecting tubules (83).

The decreased expression of AQP2 may be from a posttranscriptional defect since there were no differences in the levels of transcription of AQP2 mRNA by age in either the control or water deprivation groups (83). In all of these studies, there was a decrease response at the tubule level, whether from a decrease in abundance of V_2-receptor mRNA, abundances of AQP2 or AQP3 proteins, or a decrease in ADH binding sites that account for the decrease in urinary concentrating ability in the elderly.

The urea transporters are responsible for maintaining the countercurrent mechanism and play a major role in maximally concentrating the urine. There are 4 known urea transporters within the kidney: UT-A1, UT-A2, UT-A3, and UT-B (15,72). All have a role in the development of the tonicity in the corticopapillary gradient (72,83). Some of these urea transporters have been found to be influenced by age. With the chronic infusion of dDAVP, 30 month old rats increased their urine osmolality from 1115 ± 105 to 1868 ± 71 mOsm/kg H_2O. The change in osmolality approached levels seen in 10 month old rats. This corresponded to a 3-fold increase in urea content in the papilla (45). The change in urine osmolality corresponded to the decrease in urinary flow rate in the older rats (51). In 30 month old rats, UT-A1 protein in the inner medulla was down-regulated while there was no change in UT-A2 (51). With a chronic infusion of dDAVP there was significant upregulation of UT-A1 and UT-A2 while the abundance of UT-B was decreased. UT-A1 expression was noted to be increased in the base but not in the tip of the inner medulla (51). This may be a compensatory mechanism for the decreased amount of urea in the tip region (51).

The kidney employs a countercurrent multiplier in order to form a concentrated urine. This is dependent on the sodium chloride transporter in the water impermeable section of the kidney located in the thick ascending limb of the loop of Henle (75–76). The thin ascending limb transports NaCl by simple diffusion across the cell membrane (76). In the thick ascending limb, NaCl is actively transported by the NKCC2/BSC1 co-transporter. Ultimately, this results in an increase in the tonicity in the medulla in the presence of ADH (75,84–85). Thirty month old F344BN rats showed a significant decrease in the abundance of the NKCC2/BSC1 co-transporter in the outer medulla and a decrease in the cortical abundance of the β and γ subunits of the epithelial sodium channel (ENaC) (85). Following five days of water restriction, a significant increase in the number of NKCC2/BSC1 co-transporters was found in all age groups but less of a change was found in the older rats. A decrease in the relative abundance of the NKCC2/BSC1 co-transporter in the elderly rats would contribute to both a decrease in the ability to concentrate or dilute the urine.

These findings in the rodent kidney may be similar to the changes found in the elderly human kidney and may account for an inability to concentrate the urine. In rodents there are numerous portions of the nephron which are affected. Each alteration may play a role in the concentrating or diluting ability of the aging kidney. The decrease in abundance of UT-A1, UT-A2, and NKCC2/BSC1 transporters may all play an intricate role in the decreased ability to maintain the countercurrent multiplier system, while the decrease in abundance of AQP2 and APQ3, and V2R receptor binding, may account for the increase in water excretion. These molecular changes may be responsible for the increase in the occurrence of hypernatremia commonly observed in the elderly population..

Diluting capacity—The loss of diluting capacity occurs later and to a lesser degree than the loss of concentrating capacity in the elderly population (45). The increase in delivery of the solute load to the remaining functioning glomeruli may account for the decrease in the diluting capacity. In aging rodents the NKCC2/BSC1 co-transporter, which plays dual roles in the kidney's capacity to concentrate and dilute the urine, is down-regulated (84–85). The decrease in the reabsorption of NaCl increases solute delivery to the collecting tubule and decreases solute free water excretion.

One can conjecture that the changes in seen in rodents are likely to occur in an aging kidney without any underlying disease process. The inability to concentrate the urine can be attributed to a down-regulation of AQP2, UT-A1, and UT-A2, and a decrease of solute in the papilla. The reduction in diluting capacity has been shown both in humans and animals studies to not be as severe as concentrating ability, but still can contribute to hyponatremia under the appropriate clinical setting. Under normal conditions, healthy elderly individuals should not have considerable changes in serum sodium and the presence such changes suggests an additional cause for this clinical finding.

Salt Retention and Loss in the Elderly

Depending upon clinical conditions, elderly individuals experience either a decrease in the ability to excrete or reabsorb sodium (45,48,88–90). Because hormone levels are altered, sodium excretion is altered as well. In the elderly there is a decrease in serum renin, renin activity, and aldosterone. Under conditions of hypovolemia, the response of these hormones is blunted (88–91). The epithelial sodium channel (ENaC) in the principal cells of the collecting tubules is the major site of action for aldosterone (92). A decrease in serum aldosterone may account for an increase in excretion of sodium in the urine and an inability to decrease urinary sodium excretion in a hypovolemic state.

Atrial naturetic peptide (ANP) is produced by the atrium in response to changes in volume status (94) and blood pressure (93). Although there is an increase in the level of serum ANP in response to a volume load, the response is blunted in older rats (94). The rise in the ANP has been found not to be related to changes in levels of its mRNA (94) but may be related to a decrease in its metabolism. Similar findings are thought to occur in the elderly.

In a hypovolemic state, an inappropriate excretion of sodium is observed in the elderly that makes them more prone to hypotension (45,81) and possibly acute kidney injury (95). When 89 healthy elderly subjects were placed on a low sodium diet with normal potassium intake, they took twice as much time to conserve urinary sodium and come into neutral sodium balance as the younger adults used as controls: 17.6 ± 0.7 compared to 30.9 ± 2.8 hours (87). Because of the older kidney's inability to conserve urinary sodium, it is important to closely follow elderly patients whenever they are placed on a low salt diet in order to avoid hypotension. The role of renin, aldosterone, and ANP in the elderly in the decreased ability to conserve sodium is unknown. The elderly also require a longer time period to excrete a salt load when compared to young adults (45,86). They also have a higher likelihood of becoming volume overloaded when challenged with a sodium load. Thus, judicious use of intravenous fluids is indicated in this patient population.

Other electrolyte abnormalities in the elderly

There has not been much focus in the literature on potassium, acid base disorders, phosphorous, or magnesium. The majority of the time the plasma electrolytes are normal in the healthy elderly population unless there is undue stress. We will discuss changes in excretion of potassium and acid since they are found more commonly in the literature and the incident can be devastating and may be preventable.

Potassium—The maintenance of the serum potassium level within the normal range is influenced by various hormones, GFR, and intracellular translocation of potassium. The elderly are prescribed many medications that interfere with urinary excretion of potassium. These include potassium-sparing diuretics, angiotensin converting enzyme inhibitors, renin inhibitors, angiotensin receptor blockers, heparin, and nonsteriodal anti-inflammatory drugs. There are few studies evaluating the effect of aging on potassium excretion (18,96). Recognizing that hyperkalemia is a common occurrence in the elderly, exercising caution in the prescription of medications commonly associated with this entity may prevent its occurrence. Healthy elderly persons have a decrease in the transtubular potassium gradient compared to young adults; i.e., the elderly cannot excrete a potassium load as well as younger adults (18). Interestingly, elderly patients with chronic kidney disease can excrete a greater percentage of a potassium load as compared to a healthy elderly group (90). The reason for this decline in renal excretion in the elderly may be related to changes in hormone abundance. It has been shown in both human and animal studies that there is a decrease in serum renin and aldosterone levels (90–92). This may result in a decrease in potassium secretion by the collecting tubules in the kidney and may account for the decrease in excretion of potassium in the elderly. It may also account for the higher propensity for the elderly to become hyperkalemic with commonly prescribed medications that either directly block ENaC or further attenuate renin or aldosterone levels.

Acid Base—There are a handful of studies on acid base disorders in the elderly (19–20,97–98). Most of the elderly can maintain acid base balance under normal conditions. However, under conditions of excessive production of acid secondary to sepsis, acute kidney injury, or the administration of medications that interfere with acid secretion, an inability to maintain neutrality may be uncovered. In the elderly, there appears to be a higher concentration of hydrogen ion in metabolic acidosis which inversely correlates with serum bicarbonate and PCO_2 (19). Beckemyer et al. (20) showed that there is no change in net acid excretion capacity in young adults and children, but healthy elderly individuals could not increase net acid excretion ($NH_4 + TA - HCO_3$) in response to an increase in dietary protein, a major source of acid in the diet.

Conclusion

The kidney undergoes degenerative changes with aging, as do other organs. The histologic and functional changes in the kidney with aging may play a role in the electrolyte abnormalities observed in the elderly. The severity of these abnormalities is dependent on many factors including underlying infirmities, cognitive ability, medications, and kidney function. The awareness of these electrolyte abnormalities in the elderly population and understanding the underlying mechanisms may prevent prescribing unnecessary medications or intravenous fluids, and decreasing the morbidity and mortality associated with these interventions.

References

1. U.S. Bureau of the Census, Spencer G. Current Population Reports. Series P-25, No. 1018. Washington, D.C.: Government Printing Office; 1989. Projections of the population of the United States by age, sex and race: 1988 to 2080; p. 1-17.

2. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. JAMA 2007;298:2038–2047. [PubMed: 17986697]

3. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 2003;41:1–12. [PubMed: 12500213]

4. Melk A. Senescence of renal cells: molecular basis and clinical implications. Nephrol Dial Transplant 2003;18:2474–2478. [PubMed: 14605266]

5. Hemmelgarn BR, Zhang J, Manns BJ, et al. Progression of kidney dysfunction in the community – dwelling elderly. Kidney Int 2006;69:2155–2161. [PubMed: 16531986]

6. Anderson S, Brenner BM. Effect of aging on the renal glomerulus. Am J Med 1986;80:435–442. [PubMed: 3513560]

7. Epstein M. Aging and the kidney. J Am Soc Nephrol 1996;7:1106–22. [PubMed: 8866401]

8. Lindeman RD, Tobin JD, Shock NW. Association between blood pressure and the rate of decline in the renal function with age. Kidney Int 1984;26:861–868. [PubMed: 6533397]

9. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. J Am Geriatr Soc 1985;33:278–285. [PubMed: 3989190]

10. Baylis C, Corman B. The aging kidney: insights from experimental studies. J Am Soc Nephrol 1998;9:699–709. [PubMed: 9555673]

11. Kasiske BL. Relationship between vascular disease and age- associated changes in the human kidney. Kidney Int 1987;31:1153–1159. [PubMed: 3599655]

12. Hollenberg NK, Adams DF, Solomon HJ, Rashid A, Abrams HL, Merrill JP. Senescence in the renal vasculature in normal man. Cir Research 1974;34:309–316.

13. Fliser D, Zeier M, Nowack R, Ritz E. Renal functional reserve in healthy elderly subjects. Am J Soc Nephrol 1993;3:1371–1377.

14. Alvarez Gregori JA, MacQas Nuñez JF. Handling of water and electrolytes in the healthy old. Rev Clin Geront 2009;19:1–12.

15. Sands JM. Urine-concentrating ability in the aging kidney. Sci Aging Knowledge Environ 2003;24:PE15. [PubMed: 12844542]

16. Luckey AE, Parsa CJ. Fluid and electrolytes in the aged. Arch Surg 2003;138:1055–1060. [PubMed: 14557120]

17. Miller M. Fluid and electrolyte homeostasis in the elderly: physiological changes of ageing and clinical consequences. Baillere's Clin Endo Metab 1999;7:367–387.

18. Musso C, Liakopoulos V, De Miguel R, Imeperiali N, Algranati L. Transtubular potassium concentration gradient: comparison between healthy old people and chronic renal failure patients. Int Urol Nephrol 2006;38:387–390. [PubMed: 16868716]

19. Frassetto L, Sebastian A. Age and systemic acid-base equilibrium: analysis of published data. J Gerontol 1996;51:B91–B99.

20. Berkemyer S, Vormann J, Günther AKB, et al. Renal net acid excretion capacity is comparable in prepubescence, adolescence and young adults but falls with aging. J Am Geriatr Soc 2008;56:1442–1448. [PubMed: 18808599]

21. Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. Clinica Chimica Acta 2003;377:169–172.

22. Chumlea WC, Guo SS, Zeller CM, Reo NV, Siervogel RM. Total body water data for white adults 18 to 64 years of age: the FELS Longitudinal study. Kidney Int 1999;56:244–252. [PubMed: 10411699]

23. Watson PE, Watson ID, Batt RD. Total body water volumes for adult males and females from simple anthropometric measurements. Am J Clin Nut 1980;33:27–39.

24. Miller M. Hyponatremia and arginine vasopressin dysregulation: mechanisms, clinical consequences, and management. J Am Geriatr Soc 2006;54:345–353. [PubMed: 16460390]

25. Fried LF, Palevsky PM. Hyponatremia and hypernatremia. Med Clin North Am 1997;81:585–606. [PubMed: 9167647]

26. Snyder A, Fiegal DW, Arieff A. Hypernatremia in elderly patients: a heterogeneous, morbid, and iatrogenic entity. Ann Intern Med 1987;107:309–319. [PubMed: 3619220]

27. Anderson RJ, Chung HM, Kluge R, Schrier RW. Hyponatremia: a prospective analysis of its epidemiology and the pathogenetic role of vasopressin. Ann Intern Med 1985;102:164–168. [PubMed: 3966753]

28. Tareen N, Martins D, Nagami G, Levine B, Norris KC. Sodium disorders in the elderly. J Natl Med Assoc 2005;97:217–224. [PubMed: 15712785]

29. Palevsky PM, Bhagrath R, Greenberg A. Hypernatremia in hospitalized patients. Ann Intern Med 1996;124:197–203. [PubMed: 8533994]

30. Chassagne P, Druesne L, Capet C, Menard JF, Bercoff E. Clinical presentation of hypernatremia in elderly patients. A case control study. J Am Geriar Soc 2006;54:1225–1230.

31. Adrogué HJ, Madias NE. Hyponatremia. N Engl J Med 2000;342:1581–1589. [PubMed: 10824078]

32. Adrogué HJ, Madias NE. Hypernatremia. N Engl J Med 2000;342:1493–1499. [PubMed: 10816188]

33. Clark BA, Shannon RP, Rosa RM, Epstein FH. Increased susceptibility to thiazide-induced hyponatremia in the elderly. J Am Soc Nephrol 1994;5:1106–1111. [PubMed: 7849250]

34. Chintanadilok J, Kallas H, Lowenthal DT. Lung cancer and drug-induced severe hyponatremia. Geriatr Nephrol Urol 1998;8:161–5. [PubMed: 10221175]

35. Ranta A, Wooten GF. Hyponatremia due to an additive effect of carbamazepine and thiazide diuretics. Epilepsia 2004;45:879. [PubMed: 15230718]

36. Defronzo RA, Braine H, Colvin M, Davis PJ. Water intoxication in man after cyclophosphamide therapy time coarse and relation to drug therapy. Ann Intern Med 1973;78:861–869. [PubMed: 4713567]

37. Jacob S, Spinler SA. Hyponatremia associated with selective serotonin-reuptake inhibitors in older adults. Ann Pharmacother 2006;40:1618–1622. [PubMed: 16896026]

38. Kim GH, Lee JW, Oh YK, et al. Antidiuretic effect of hydrochlorothiazide in lithium-induced nephrogenic diabetes insipidus is associated with upregulation of aquaporin-2, Na-Cl co-transporter, and epithelial sodium channel. J Am Soc Nephrol 2004;15:2836–43. [PubMed: 15504936]

39. Famularo G, Gasbarrone L, De Virgilio A, Minisola G. Mirtazapine-associated hyponatremia in an elderly patient. Ann Pharmacother 2009;43:1144–1145. [PubMed: 19435965]

40. Sarret D, Le Berre JP, Zemraoui N. Tramadol-induced hyponatremia. Am J Kidney Dis 2008;52:1026. [PubMed: 18971023]

41. Palmer BF, Gates JR, Lader M. Causes and management of hyponatremia. Ann Pharmacother 2003;37:1694–1702. [PubMed: 14565794]

42. Terzian C, Frye EB, Piotrowski ZH. Admission hyponatremia in the elderly: factors influencing prognosis. J Gen Intern Med 1994;9:89–91. [PubMed: 8164083]

43. Sajadieh A, Binici ZB, Mouridsen Z, et al. Mild hyponatremia carries a poor prognosis in community subjects. Am J Med 2009;12:679–686. [PubMed: 19559171]

44. Dontas AS, Marketos SG, Papanayioutou P. Mechanism of renal tubular defects in old age. Postgrad Med J 1972;48:295–303. [PubMed: 18557242]

45. McAloon Dyke M, Davis M, Clark BA, Fish C, Elahi D, Minaker KL. Effect of hypertonicity in water intake in elderly : an age –related failure. Geriatr Nephrol Urolol 1997;7:11–16.

46. Stachenfeld NS, Mack GW, Takamata MA, DiPertro L, Nadel ER. Thirst and fluid regulatory responses to hypertonicity in older patients. Am J Physiol 1996;271:R757–R765. [PubMed: 8853401]

47. Crowe MJ, Forsling ML, Rolls BJ, Phillips PA, Ledingham JGG, Smith RF. Altered water excretion in healthy elderly men. Age Aging 1987;16:285–293.

48. Davies I, O'Neill PA, McLean KA, Catania J, Bennett D. Age-associated alterations in thirst and arginine vasopressin in response to water or sodium load. Age Aging 1995;42:151–159.

49. Kirkland J, Lye M, Goddard C, Vargas E, Davies I. Plasma arginine vasopressin in dehydrated elderly patients. Clin Endocrinol 1984;20:451–456.

50. Schmidt-Nielsen B, Barrett JM, Graves B, Crossley B. Physiological and morphological responses of rat kidney to reduced dietary protein. Am J Physiol 1985;248:F31–F42. [PubMed: 3970163]

51. Combet S, Geffroy N, Berthonaud V, et al. Correction of age-related polyuria by dDVAP: molecular analysis of aquaporin and urea transporters. Am J Physiol Renal Physiol 2003;284:F199–F208. [PubMed: 12388383]

52. Kishore BK, Krane CM, Reif M. Molecular physiology of urinary concentration defect in elderly population. Int Urol Nephrol 2001;33:235–248. [PubMed: 12092636]

53. Schrier RW. Water and sodium retention in edematous disorders: role of vasopressin and aldosterone. Am J Med 2006;119:S 47–53.

54. Ishikawa SE, Saito T, Fukagawa A, et al. Close association of urinary excretion of aquaporin-2 with appropriate and inappropriate arginine vasopressin –dependent antidiuresis in hyponatremia in elderly subjects. J Clinic Endocrinol Metab 2002;86:1665–1671.

55. Brownstein MJ, Russell JT, Gainer H. Synthesis, transport and release of posterior pituitary hormones. Science 1980;207:373–378. [PubMed: 6153132]

56. Land H, Schutz G, Schmale H, Ritcher D. Nucleotide sequence of cloned cDNA encoding bovine arginine vasopressin-neurophysin II precursor. Nature 1982;295:299–303. [PubMed: 6276766]

57. Dunn FL, BrennanT J, Nelson AE, Robertson GL. The role of blood osmolality and volume in regulating vasopressin secretion in the rat. J Clin Invest 1973;52:3212–3219. [PubMed: 4750450]

58. Swaminathan S. Osmoreceptors or sodium receptors: investigation into ADH release in rhesus monkey. J Physiol 1980;307:71–83. [PubMed: 7205680]

59. Rai A, Whaley-Connell A, McFarlane S, Sowers JR. Hyponatremia, arginine vasopressin dysregulation, and vasopressin receptor antagonism. Am J Nephrol 2006;26:579–589. [PubMed: 17170524]

60. Musso C, Vassilios L, Pangre N, et al. Renal physiology in elderly persons with severe immobility syndrome. Int Urol Nephrol 2009;41:437–441. [PubMed: 19277889]

61. Gottschalk CW, Mylle M. Evidence that mammalian nephron function as a countercurrent multiplier system. Science 1958;128:594. [PubMed: 13580223]

62. Agre P. The aquaporin water channels. Proc Am Thorac Soc 2006;3:5–13. [PubMed: 16493146]

63. Ma T, Yang B, Gillespie A, Carlson EJ, Epstein CJ, Verkman AS. Severely impaired urinary concentrating ability in transgenic mice lacking aquaporin-1 water channels. J Bio Chem 1998;273:4296–4299. [PubMed: 9468475]

64. Preston GM, Smith BL, Zeidel ML, Moulds JJ, Agre P. Mutations in aquaporin-1 in phenotypically normal humans without functional CHIP water channels. Science 1994;265:1585–1587. [PubMed: 7521540]

65. Knepper MA. The aquaporin family of molecular water channels. Proc Nalt Acad Sci USA 1994;91:6255–6258.

66. Hayashi M, Sasaki S, Tsuganezawa H, et al. Expression and distribution of aquaporin of collecting duct are regulated by vasopressin V2 in rat kidney. J Clin Invest 1994;94:1778–1782. [PubMed: 7525648]

67. Nielsen S, DiGiovanni SR, Christensen EI, Knepper MA, Harris HW. Cellular and subcellular immunolocalization of vasopressin-regulated water channel in rat kidney. Proc Natl Acad Sci USA 1993;90:11663–11667. [PubMed: 8265605]

68. Nielsen S, Chou CL, Marples D, Christensen EI, Kishore BK, Knepper MA. Vasopressin increases water permeability of kidney collecting duct by inducing translocation of aquaporin-CD water channels to plasma membrane. Proc Natl Acad Sci USA 1995;92:1013–1017. [PubMed: 7532304]

69. Pedersen RS, Bentzen H, Bech JN, Pedersen EB. Effect of water deprivation and hypertonic saline infusion on urinary AQP2 excretion in healthy humans. Am J Physiol Renal Physiol 2001;280:F860–867. [PubMed: 11292629]

70. Lu HJ, Matsuzaki T, Bouley R, Hasler U, Qin QH, Brown D. The phosphorylation state of serine 256 is dominant over that of serine 261 in the regulation of AQP2 trafficking in renal epithelial cells. Am J Physiol 2008;295:F290–F294.

71. Bagnasco SM. Role and regulation of urea transporters. Pflüger Arch-Eur J Physiol 2005;450:217–226.

72. Sands J. Renal urea transporters. Curr Opin nephrol Hyperten 2004;13:525–532.

73. Gottschalk CW, Lassiter WE, Mylle M, Ullrich KJ, Schmidt-Nielsen B, O'Dell R, Pehling G. Micropuncture study of composition of loop of Henle fluid in desert rodents. Am J Physiol 1962;204:532–535. [PubMed: 13949504]

74. Kim GH, Ecelbarger CA, Mitchell C, Packer RK, Wade JB, Knepper MA. Vasopressin increased Na-K-2Cl co-transporter expression in thick ascending limb of Henle's loop. A J Physiol Renal Physiol 1999;270:F96–F103.

75. Knepper MA, Kim G-H, Fernandez-Llama P, Ecelbarger CA. Regulation of thick ascending limb transport by vasopressin. J Am Soc Nephrol 1999;10:628–634. [PubMed: 10073614]

76. Imai M, Kokko JF. Mechanism of sodium and chloride transportation thin ascending limb of Henle. J Clin Invest 1976;58:1054–1060. [PubMed: 993330]

77. Thunhorst RL, Johnson AK. Thirst and salt appetite responses in young and old Brown Norway rats. Am J Physiol 2003;28:R317–R327.

78. Rowland NE, Morien A, Garcea M, Fregly MJ. Aging and fluid homeostasis in rats. Am J Physiol 1997;273:R1441–R1450. [PubMed: 9362310]

79. Swenson KL, Sands JM, Jacobs JD, Sladek CD. Effect of aging on vasopressin and aquaporin responses to dehydration in Fischer 344-Brown-Norway F1 rats. Am J Physiol Regul Integr Comp Physiol 1997;273:R35–R40.

80. Combet S, Teillet L, Geelen G, et al. Food restriction prevents age-related polyuria by vasopressin – dependent recruitment of aquaporin-2. Am J Physiol Renal Physiol 2001;281:F1123–F1131. [PubMed: 11704564]

81. Preisser L, Teillet L, Aliotti S, et al. Down regulation of aquaporin-2 and -3 in aging kidney is independent of V2 vasopressin receptor. Am J Physiol Renal Physiol 2000;279:F144–F152. [PubMed: 10894796]

82. Tian Y, Serino R, Verbalis JG. Down regulation of renal vasopressin receptor and aquaporin -2 expression parallels age –associated defects in urine concentration. Am J Physiol Renal Physiol 2004;287:797–805.

83. Combet S, Gourand S, Gobin R, Berthonaud V, Geelen G, Corman B, Verbavatz JM. Aquaporin-2 downregulation in the kidney medulla of aging rats is posttranscriptional and is abolished with water deprivation. Am J Physiol Renal Physiol 2008;284:F1408–F1414. [PubMed: 18367658]

84. Di Stefano A, Wittner M, Corman B. Vasopressin stimulation of NaCl transport in the medullary thick ascending limb of Henle's loop is decreased in aging mice. Pfügers Arch 1991;419:327–331.

85. Tian Y, Riazi S, Khan O, et al. Renal ENaC subunit, Na-K-2Cl and Na-Cl cotransporter abundances in aged, water-restricted F344 × Brown Norway rats. Kidney Int 2006;69:304–312. [PubMed: 16408120]

86. Luft FC, Weinberger MH, Fineberg NS, Miller JZ, Grim CE. Effect of age on renal sodium homeostasis and its release to sodium sensitivity. Am J Med 1987;82:9–15. [PubMed: 3544837]

87. Epstein M, Hollenberg NK. Age as a determinant of renal sodium conservation in normal man. J Lab Clin Med 1976;87:411–417. [PubMed: 1249474]

88. Jung FF, Kennefick TM, Ingelfinger JR, Vora JP, Anderson S. Down-regulation of the intrarenal renin-angiotensin system in the aging rat. J Am Soc Nephrol 1995;5:1573–1580. [PubMed: 7756590]

89. Corman B, Barrault MB, Klinger C, et al. Renin gene expression n the aging kidney: effect of sodium restriction. Mech Ageing Dev 1995;84:1–13. [PubMed: 8719773]

90. Trenkwalder P, James GD, Laragh JH, Sealey JE. Plasma renin activity and plasma prorenin are not suppressed in hypertension screening to old age. Am J Hypertens 1996;9:621–627. [PubMed: 8806973]

91. Weidmann P, De Myttenaere- Burszstein S, Maxwell MH, de Lima J. Effect of aging on plasma renin and aldosterone in normal man. Kidney Int 1975;8:325–333. [PubMed: 538]

92. Ling BN, Kemendy AE, Kokko KE, Hinton CF, Marunaka Y, Eaton DC. Regulation of the amiloride-blockable sodium channel from epithelial tissue. Mol Cell Biochem 1990;99:141–150. [PubMed: 1962846]

93. Pollack JA, Skvorak JP, Nazian SJ, Landon CS, Dietz JR. Alterations in atrial natriuretic peptide (ANP) secretion and renal effects in aging. J Gerontol A Biol Sci 1997;52 :B196–B202.

94. Sagnella GA, Markandu ND, Shore AC, MacGregor GA. Raised circulating levels atrial natriuretic peptides in essential hypertension. Lancet 1986;327:179–181. [PubMed: 2868206]

95. Abuelo JG. Normotensive ischemic acute renal failure. N Engl J Med 2007;357:797–805. [PubMed: 17715412]

96. Musso CG, Miguel R, Algranati L, Dos Ramos Farias E. Renal potassium excretion: comparison between chronic renal disease patients and old people. Int Urol Nephrol 2005;37:167–170. [PubMed: 16132781]

97. Rylander R, Remer T, Berkemyer S, Vormann J. Acid- base status affects renal magnesium losses in healthy, elderly person. J Nut 2006;136:2374–2377.

98. Agarwal BN, Cabebe FG. Renal Acidification in elderly subject. Nephron 1980;26:291–295. [PubMed: 7453916]
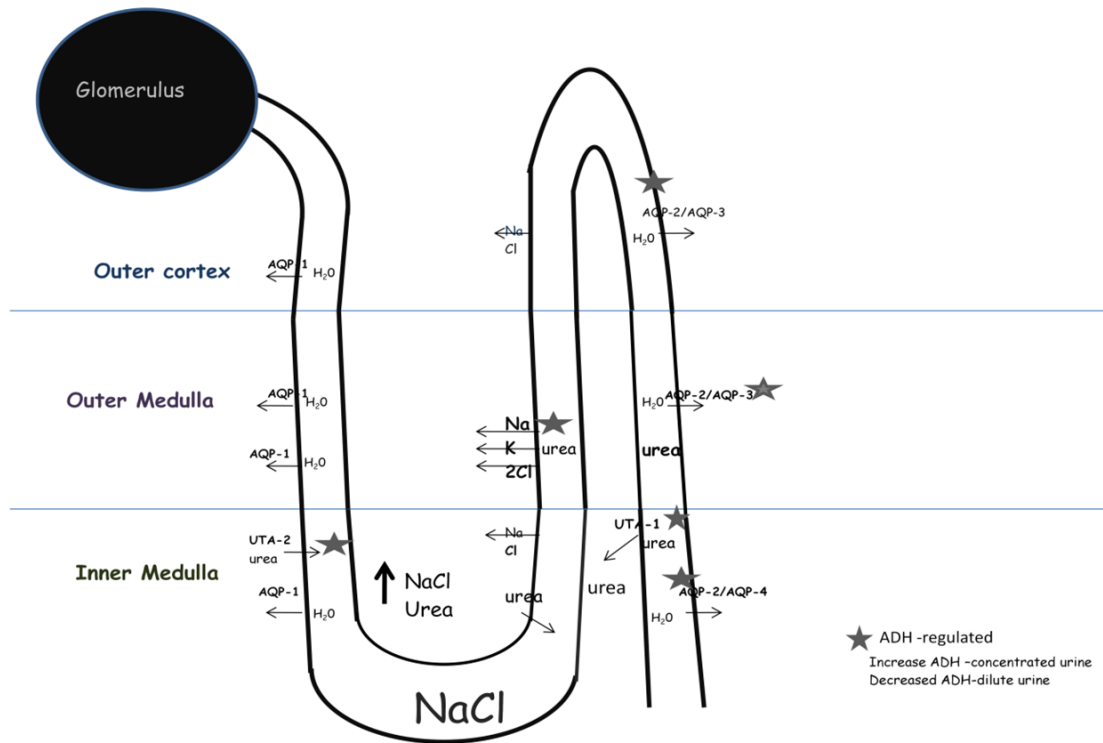
Fig 1.
Under normal conditions the various transporters/co-transporters and water channels play a role in water balance. The UT-A1 urea transporter, AQP2, AQP3, and NKCC2/BSC1 transporters are influenced by ADH secretion. The selective permeability of the loop of Henle to water and the medullary thick ascending loop to NaCl allows for the creation of the countercurrent system. The presence of AQP2 and the high concentration of NaCl and urea in the inner medulla allows for the reabsorption of water free solute in the collecting tubules for the final concentrated urine. The selective permeability of the NKCC2/BSC1 co-transporter in the medullary thick ascending limb permits the formation of dilute urine.
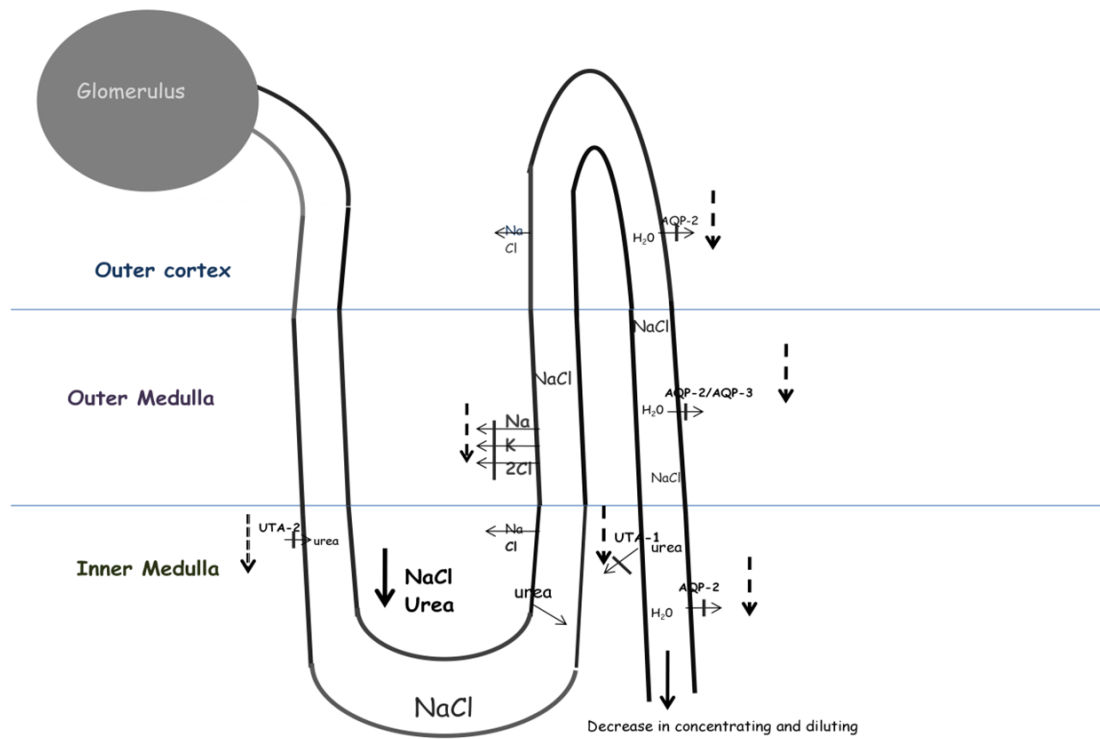
Fig 2.
The putative changes in the renal transport system in the elderly are shown. In animal studies there is a decrease in the abundance of AQP2, AQP3, NKCC2/BSC1 and UT-A1, A2, A3. The arrrows represent the transporters and water channels known to be downregulated in animal studies. These changes may be present in the elderly population affecting the diluting and concentrating capacity.

Table 1

Commonly Prescribed Medications Associated with Hyponatremia and Hypernatremia in the Elderly[*]

Hyponatremia	Mechanism
Prostaglandin-synthesis inhibitors	Impair water excretion
Phenothiazines	Release of ADH
Tricyclics	Release of ADH
Serotonin-reuptake inhibitors	Release of ADH or Potentiates renal ADH effect
Opiate derivatives	Release of ADH
Carbamazepine	Release of ADH
Cyclophosphamide	Potentiates renal ADH effect
Thiazides	Na loss, decrease distal fluid delivery, ADH release
Desmopressin	V_2R agonist
Hypernatremia	
Lithium	Decrease AQP-2
Vasopressin V_2 receptor antagonists	Decrease cAMP
Loop diuretics	Decrease diluting capacity
Mannitol	Osmotic diuresis

[*] References 28_41