İstanbul Med J 2017; 18: 53-7
DOI: 10.5152/imj.2017.26928

Review

Aging and the Kidneys

Fatih Dede, Canan Yazıcı Özgür

Abstract

Various anatomical and physiological changes occur in the kidneys on aging. Systemic hemodynamics in kidney functioning, which is quite important in aging-induced adaptation to these changes, undermines the ability of the kidneys. Acute kidney injury and fluid balance in the head, including the development of the deterioration of many older patients with kidney disease, are much more frequently observed. There is an increase in the frequency of comorbid diseases and related drug use in this age group. Many causes of renal pathology have emerged.

Keywords: Acute kidney injury, aging, kidneys

With socioeconomic development, the access to health services has become widespread. With the expansion of an effective and efficient health care network, the elderly population continues to grow, especially in developed countries. As a result, new approaches in the field of nephrology are required, as in every other branch.

Along with aging, various anatomical and physiological changes occur in the kidney. These changes become evident particularly after the fourth decade, and they include not only structural, but also functional changes (tubular and glomerular functions). The changes that occur with aging weaken the adaptability of kidney, which plays a very important role in systemic hemodynamics. Many kidney diseases are more easily and frequently observed in elderly patients, especially in case of impaired fluid balance and development of acute renal damage (ARD). These changes that accompany aging facilitate the development of new kidney pathologies, particularly in the presence of additional disorders that can lead to kidney disease, such as diabetes mellitus (DM), atherosclerotic vascular diseases, and hypertension (HT). Chronic kidney disease (CKD) is an important problem observed in the elderly population; the complications associated with CKD are more common in the elderly patients when compared to younger patients. Especially in the presence of additional comorbid conditions, there are many difficulties present in managing these complications (1, 2). Although there is no accelerating factor in approximately 5% to 10% of the population, there is a decrease in renal function with age, and there is no measurable reduction in 30% (3).

Structural Changes

The kidney mass increases with age and reaches the maximum weight and volume in the third decade. Starting with the fourth decade, the kidney mass begins to decrease, especially in the cortex. The kidney mass, which ranges from 200 g to 270 g at the age of 30, decreases at a rate of 20%–30% to 180 g–200 g at the age of 90. The loss of cortex tissue occurs with the loss of nephron function and decrease in glomerular filtration rate (GFR). Focal sclerosis and glomerular basement membrane thickening were detected in autopsies of individuals without renal disease. Sclerosis or hyalinization in the glomeruli starts at the age of 30. While the rate of fully sclerosed glomeruli was found to be 1%–2% at the age of 30 under the light microscope, this rate reaches 10%–12% on average at the age of 70 (2–5). Total glomerular volume increases with aging. An increase in endothelial and mesangial cells accompany this increase. An increase in the number of mesangial cells and an increase of mesangial matrix are thought to be a benign process. Podocytes are postmitotic and do not replicate. As a result, the ratios in total glomerulus volume decrease (5, 6). While aging is accompanied by thickening of tubule cell membrane, tubular atrophy and interstitial fibrosis together with the loss of glomeruli due to the loss of cortex, hypertrophy, and hyperplasia develop in the atrophic nephrons, especially in the proximal tubules (4). There have been no significant changes observed in the structure of the distal tubule with aging. Intimal thickening and concomitant sclerosis in the arterioles and large vessel walls are the changes depending on aging that is observed in the vascular bed (7).

Department of Nephrology, University of Health Sciences, Ankara Numune Training and Research Hospital, Ankara, Turkey

Address for Correspondence:
Fatih Dede
E-mail: fatded@yahoo.com

Received: 18.08.2016

Accepted: 09.11.2016

Functional Changes

With aging, the kidney physiology changes as well. The GFR has been shown to decrease by 0.8 mL/min/year every year from the age of 30 onwards (8). This decrease in GFR is associated with the decrease in the number of nephrons (3, 9). While the renal plasma flow is 600 ml/min at the age of 30, it declines to 300 ml/min at the age of 80, decreasing 10% per each decade. This decrease is accompanied by an increase in both afferent and efferent arteriolar resistances (10). The ability to modulate renal medullary oxygenation has been shown to reduce in functional magnetic resonance imaging in elderly volunteers. This reduction may be due to changes in the renal autocrine system (prostaglandins, dopamine, nitric oxide, natriuretic peptides, or endothelin) or vascular changes. As a result, there is an increased susceptibility to ischemic ARD in the aging kidney (3, 11). The most important changes observed with aging in tubular function are the reduction in the ability of urine concentration and acidification. Decrease in the concentration may be associated with inadequate response to intrinsic defects or antidiuretic hormone (ADH) in the tubular epithelium (3, 9).

Serum creatinine levels are not a healthy indicator of GFR that decreases with age, because the muscle mass also decreases with age similar to GFR. While muscle mass is 19% of body weight at the age of 25, this rate regresses to about 12% at the age of 70 (12). Therefore, this should be taken into consideration when adjusting medication especially in elderly patients, and it should be kept in mind that there may be a significant decrease in GFR without an increase in serum creatinine concentration (13). In 1999, the Modification of Diet Renal Disease (MDRD) formula was started to be used for GFR calculation. However, the fact that this formula includes the patient population from 18 to 70 years limits its use in the elderly (13). Creatinine clearance formulas that were calculated using the MDRD formula, the Cockcroft Gault formula, iothalamate clearance, and 24-hour urine volume were compared in the studies including the elderly, and there were significant differences observed. As a result, the gold standard was determined to be the iothalamate clearance (9, 14). However, because this process is expensive and the practical daily use is limited, the most reliable results are obtained with creatinine clearance formula calculated using 24-hour urine volume (9).

FORMULA 1. By collecting urine for 24 hours (15);
Creatinine clearance (ml/min)=$urine_{creatinine}$ (mg/dL) x Daily urine volume (mL)/$serum_{creatinine}$ (mg/dL) x 1440

FORMULA 2. Only by examining $serum_{creatinine}$ (Cockcroft-Gault formula) (16)
Creatinine clearance = (140-Age) x (Ideal weight)/ Serum creatinine (mg/dL) x 72
The value found in women is multiplied by 0.85.
Ideal weight (for male)= 50+2.3 x Height(cm)-152.4) / 2.54
Ideal weight (for woman) = 45.5+2.3 x Height(cm)-152.4) / 2.54

Liquid–Electrolyte/Acid-Base Balance

Approximately 60% of body weight in a healthy young man and 52% in a healthy young woman consists of water. In the age group of 65 and over, this rate decreases to 54% in males and 46% in females (17). A decrease in body water percentage along with aging increases the predisposition of elderly individuals to dehydration (18).

Along with aging, due to an increased absorption of distal tubule sodium and medullary blood flow associated with a decrease in GFR, maximum concentration and dilution ability of the kidney diminishes (19). While the mean osmolality is 1109 mOsm/kg H_2O, and minimum urine osmolality is 52 mOsm/kg H_2O in persons younger than 40, these values are 882 mOsm/kg H_2O and 92 mOsm/kg H_2O, respectively, in persons older than 60 (20).

A decrease in GFR that accompanies aging, interstitial fibrosis, a decrease in basal renin activity and aldosterone levels, and an inadequate target organ response to ANP lead to a decrease in sodium reabsorption from the distal tubules; consequently, there is an imbalance between dietary sodium uptake and urinary sodium loss (21-23). While the risk of hypernatremia increases because the response to thirst weakens in individuals over the age of 65 (24), hyponatremia can easily develop with the application of thiazide group diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs) (25). As a result of aging and a muscle mass decrease, a total amount of body and variable potassium decreases (26). A decreased activity of Na^+/K^+-ATPase that occurs with aging causes a decrease in the kaliuretic response. Clinical trials have shown that the risk of hyperkalemia is higher in elderly individuals due to the use of potassium-sparing diuretics, beta-blockers, angiotensin-converting enzyme inhibitors (ACE-I), ketoconazole, and cyclosporine (27). At the same time, diuretic-induced hypokalemia is more common in elderly patients (28). It has been found that, along with aging, the activity of the 1-α hydroxylase enzyme in the kidney decreases (29), no change occurs in calcium reabsorption from the kidneys, and phosphorus reabsorption decreases, especially after the restriction of calcium and phosphorus in the diet (30).

Although the blood pH and HCO3 concentration in the elderly are within normal limits, as a consequence of anatomical or functional changes in tubules with aging, the ammonium excretion decreases, and the response of the kidney to adaptation deteriorates, especially when the acid load suddenly increases (17).

KIDNEY DISEASES IN THE ELDERLY

Acute Kidney Injury

Depending on the anatomical and physiological changes developing in the kidney with aging, in addition to the insufficiency of adaptation mechanisms of the kidney, the frequency of comorbid diseases, increase in the number of drug use, and the pathologies that cause obstructive uropathy, which is common in the elderly population, especially in male patients, increase the predisposition to AKI (31, 32).

The most common cause of AKI in the geriatric age group is prerenal azotemia. In this age group, in addition to the decrease in renal blood flow and GFR, atherosclerotic vascular disease that is already existing, especially poor fluid intake or loss, reduced cardiac output, medications (NSAIDs, ACE-I, angiotensin receptor blockers [ARB]), and situations such as fluid redistribution also increase predisposition to AKI depending on azotemia (30, 33). NSAID-associated AKI is more common in the elderly than in the general population. Prostaglandins play an important role in renal autoregulation. The decrease in prostaglandin inhibition and glomerular blood flow associated with the use of NSAIDs significantly increases the risk of developing AKI, particularly in the cases of concomitant intravascular volume decrease or decreased total

body water. Similar effects are valid for other drugs (ACE-I) that affect intrarenal hemodynamics and renal autoregulation through different mechanisms (34, 35).

Acute glomerulonephritis, acute tubulointerstitial nephritis (ATIN), and renovascular diseases are the most common causes of renoparanchymal AKI in elderly patients. In patients in whom biopsy was performed, the most common histopathology is rapidly progressive (crescentic) glomerulonephritis (RPGN). Vasculitis and idiopathic crescentic glomerulonephritis constitute more than half of these cases (31, 33). Acute tubular necrosis (ATN) develops as a result of the exposure to prolonged renal ischemia or nephrotoxins. Renal hypoperfusion and the factors leading to ischemia are closely related to ATN. Intraoperative hypotension, peripapillary fluid loss, and arrhythmias in major surgical procedures constitute one-third of the ATN cases. Radiocontrast and aminoglycoside use are the other important etiologic factors (32, 35). Cholesterol embolism is also among the causes of AKD in elderly patients. It may be spontaneous, and cholesterol crystals may occlude small renal arteries by splitting off the atherosclerotic plaques, especially after cardiac catheterization and aortic angiography (36). Although less frequently seen; rhabdomyolysis, infections, cerebrovascular events, crush syndromes, hyperosmolar causes, hypothermia, and trauma may cause ATN development in elderly patients (37).

Approximately 5% of elderly patients with acute renal failure have postrenal causes. Benign prostatic hyperplasia, prostate carcinoma, retroperitoneal or pelvic neoplasms (such as non-Hodgkin lymphoma), neurogenic bladder, bladder, cervix, ovarian, and rectum cancers are common causes of postrenal AKI in elderly patients. Early diagnosis and opening of the obstruction are very important in the preserving of renal functions in postrenal AKI. In case of a complete obstruction lasting more than 4 weeks, the incidence of permanent renoparanchymal injury increases (32, 37).

In elderly patients with acute renal injury, the anamnesis is quite suggestive, as in young patients. The volume status of the patient should be well assessed, and the examination in the etiology should be done in detail. The parameters suggesting potential nephrotoxic drug presence and obstruction should be carefully assessed. Because of a prominent decrease in urine concentration ability that occur with aging, the reliability of urine indexes such as urinary sodium concentration and fractionated sodium excretion, which are applied to in the case of prerenal azotemia, is reduced. The most reliable method for the diagnosis of prerenal AKI in elderly patients is hourly urine response to appropriate fluid replacement and the follow-up of renal functions. Ultrasonography (USG) is a good method that shows obstructions. It is quite valuable in evaluating the size and parenchyma of the stone, mass, and kidney (38).

Renal biopsy should be planned in case of absolute anuria when no obstruction can be detected; a systemic disease such as vasculitis, which can significantly change the treatment with the diagnosis; AKI developing during the kidney transplantation; and RPGN, ATIN, and prolonged oliguria/AKI (>4 weeks) whose etiologic factor is unknown. Advanced age is not a contraindication for kidney biopsy alone (31, 38).

The treatment approaches to AKI in elderly patients are similar to those in the general population. Providing adequate intravascular volume is necessary to maintain renal blood flow. Proper heart catheterization and hemodynamic monitoring may be necessary in critical patients. Dopamine, phenoldopam, which is a dopamine 1 receptor agonist, combinations of α and β adrenergic agonists, calcium channel blockers, mannitol, norepinephrine, different peptides, and growth factors all have been used in the treatment of AKI but have not shown any absolute benefits. Since the number of comorbid diseases in these patients is high, and the catabolic process significantly increases in the presence of AKI, nutritional support should be planned effectively (9, 38).

In cases when renal replacement therapy is required, the dialysis method, dialysis dose, and the starting time of dialysis have not been shown to be associated significantly with the survival of the kidney and patient. Each patient should be assessed separately in terms of volumetric status and solute clearance targets, and dialysis dose should be planned taking other accompanying catabolic processes into consideration. Continuous and slow-flow methods may be preferred for hemodynamically instable patients, for those with high intracranial pressure, and for the removal of medium molecular weight toxins (33, 38).

Glomerular Diseases

Glomerulonephritis is the third most common cause of the end-stage renal disease (ESRD). When its close relationship with renal survival is considered, an effective treatment is of great importance, following a rapid and accurate diagnosis. Elderly patients diagnosed with biopsy-proven glomerulonephritis may present with the following forms of disease upon admission (39, 40):

1. Asymptomatic urinary abnormalities
2. Acute nephritic syndrome or acute glomerulonephritis: hematuria, nonnephrotic proteinuria, reduction in GFR, water and salt retention, hypertension, and AKI
3. Rapidly progressive glomerulonephritis: acute onset, progressive loss of renal function, frequent oliguria, and systemic findings (pulmonary and skin involvement)
4. Nephrotic syndrome: severe proteinuria, edema, hyperlipidemia $\pm$ hypertension, AKI
5. Chronic glomerulonephritis: progressive clinical course, proteinuria at different degrees, hematuria, hypertension, and AKI

In addition to the thickening of glomerular basement membrane and the narrowing of the glomerular surface area that occur with aging, the rise in the prevalence of autoantibody and immunocomplexes increases immunocomplex-mediated glomerular injury risk (40, 41).

Acute glomerulonephritis and RPGN are common forms in elderly patients, especially those with AKI. Postinfectious glomerulonephritis was detected in 6%–8% of geriatric patients. While clinical features resemble the young population, the incidence of hypertension, azotemia, and ESRD is higher in geriatric population (31, 40). The most frequent pathologic finding in kidney biopsies of the patients in whom RPGN is detected is isolated primary pauci-immune glomerulonephritis. ANCA (mostly pANCA) is positive in approximately 45%-55% of these cases. Histological findings of small-vessel vasculitis outside the kidney were detected in 20%-25%. Most of the remaining patients are patients with cANCA-related Wegener's granulomatosis in whom pulmonary involvement accompanies the clinic. The presence of infection, drug use, pres-

ence of hepatitis C, cryoglobulinemia, and Henoch-Schönlein Purpura should absolutely be kept in mind as secondary causes in patients diagnosed with RPGN. ANCA was not detected in 10%-20% of patients with isolated primary pauci-immune glomerulonephritis (39). In the presence of RPGN, the combination of corticosteroids and cyclophosphamide is most commonly used in treatment, as in other age groups. Although elderly patients were shown to have a significantly lower 5-year survival compared to younger patients (31% and 83%, respectively), and despite the high side effects of cytotoxic and corticosteroid treatments, renal survival is outstanding in patients receiving treatment (39-41).

All of the primary glomerular diseases, especially membranous glomerulonephritis, can be found in patients with diagnosed nephrotic syndrome. While secondary glomerular diseases due to amyloidosis and diabetic nephropathy are more frequently observed in patients with heavy proteinuria, the etiologic causes of secondary etiologic factors such as malignancies (especially lung, colon), chronic infectious diseases, and drugs should be investigated in these patients. IgA nephritis is not often seen in elderly patients. Despite higher albumin levels in patients in whom nephrotic syndrome is detected, hypercoagulability and associated thromboembolic complications are more frequently observed, in addition to an increase in the frequency of edema (42).

Renovascular Diseases

Atherosclerosis-related renovascular diseases are among the causes of secondary hypertension and acute/chronic kidney damage (ischemic nephropathy) that are observed in the elderly population and should not be ignored. Ischemic nephropathy is defined as a reduction in GFR, resulting from partial or complete luminal obstruction of the preglomerular renal arteries. Depending on the level of renal perfusion reduction, it may occur in different clinical forms as uncontrolled HT, AKI, CKD, and/or AKI in the basis of CKD. In patients with advanced renovascular disease, AKI has been shown to develop in 6%–38% of patients with the use of ACE-I/ARB treatment. The incidence of renovascular hypertension in the entire hypertensive patient population is 2%-3%. A stenosis (75%-80%) at the level that can initiate events leading to the development of renal tissue ischemia and hypertension is considered to be a significant renovascular disease. Newly diagnosed hypertension, inability to take the blood pressure under control during treatment, the presence of diffuse atherosclerotic vascular disease, the development of AKI after starting the ACE-I and/or ARB treatment, the presence of unknown azotemia, recurrent pulmonary edema, Grade 3-4 hypertensive retinopathy, hypokalemia deepening with the use of diuretics, and renal artery stenosis in the presence of microangiopathic hemolytic anemia should be considered after the age of 50 (43, 44).

Atheroembolic renal disease is azotemia caused by preglomerular ischemia. In general, atheroembolic disease should be considered in the presence of eosinophilia accompanying AKI, purpuric-ischemic skin lesions and severe proteinuria that can be at nephrotic level. The patients in whom endovascular intervention is applied, particularly for diagnostic or therapeutic purposes, should be closely monitored for cholesterol embolism (9, 43).

Tubulointerstitial Diseases

Several histological changes that include interstitial fibrosis and mononuclear cell infiltration developing in tubulointerstitial localization due to aging may cause clinical changes consistent with tubulointerstitial nephritis in the presence of infectious agents, physical, chemical/toxic, and immunological agents affecting particularly this area (9). The pattern of tubular dysfunction changes according to the anatomical location of the injury. Proximal tubular involvement is characterized by the Fanconi syndrome (bicarbonaturia, glucosuria, hyperuricosuria, hyperphosphatry, and aminoaciduria). Whereas distal tubular lesions are associated with distal tubular acidosis, the ability to secrete potassium, and the decrease in sodium reabsorption, medullary lesions involving the papillae occur with the loss of salt and the decrease in the ability of the kidney to concentrate urine at a maximum level. In ATIN etiology, hypersensitivity reactions associated with infectious agents and medicines (primarily antibiotics such as penicillin and cephalosporin group and NSAIDs) are the most frequently described as the cause in elderly patients, as well as in other age groups (45).

Chronic Kidney Disease

Chronic kidney disease (CKD), which is defined as the presence of structural, imaging, or laboratory findings indicating renal damage for at least 3 months with or without reduction in GFR, or the detection of GFR<60 mL/min/1.73 m^2 with or without renal injury for at least 3 months, shows the same symptoms and findings in elderly patients as in the general population (9). Considering the co-morbidities accompanying advanced age, the risk of cardiovascular disease is increased. Renal osteodystrophy, which begins to be observed particularly in Stage 3 CKD, causes an increase in morbidity due to bone fracture, weight loss, and soft tissue calcification in elderly patients. Anemia and associated left ventricular hypertrophy, congestive heart failure, and myocardial ischemia increase mortality in elderly patients with CKD (46-48). Hemodialysis is still the most preferred renal replacement therapy option in the world for Stage 5 CKD. According to the Turkish national nephrology, dialysis and transplant registry system report for 2014, 43% of the hemodialysis patients are over 65 years of age, and 17.5% of them are over 75 years of age (49).

Aging is an important process that affects all systems in the body. Anatomical and functional changes in age-related functional renal mass occur with inadequate adaptation in kidney response, especially to systemic hemodynamic changes. An increase in the frequency of comorbid diseases and related drug use in this age group lead to more frequent and complex confrontation of many renal pathologies, especially AKI and fluid/electrolyte disorders. When evaluated in this context, a close follow-up is crucial for renal survival, cost, and patient morbidity and mortality, especially in elderly patients having the risk factors for renal parenchymal disease development, and in the presence of pathologies that newly emerge and require additional treatment.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.D., C.Y.Ö.; Design - F.D., C.Y.Ö.; Supervision - F.D., C.Y.Ö.; Analysis and/or Interpretation - F.D.; Literature Search - F.D.; Writing Manuscript - F.D., C.Y.Ö.; Critical Review - F.D., C.Y.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Hansberry MR, Whittier WL, Krause MW. The elderly patient with chronic kidney disease. Adv Chronic Kidney Dis 2005; 12 : 71-7. [CrossRef]
2. Epstein M. Aging and the kidney. J Am Soc Nephrol 1996; 7: 1106-22.
3. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. J Am Geriatric Soc 1985; 33: 278-85. [CrossRef]
4. Kappel B, Olsen S. Cortical interstitial tissue and sclerosed glomeruli in the normal human kidney, related to age and sex. A quantitative study. Virchows Arch A 1980; 387: 271-7. [CrossRef]
5. Kaplan C, Pasternack B, Shah H, Gallo G. Age-related incidence of sclerotic glomeruli in human kidneys. Am J Pathol 1975; 80: 227-34.
6. Kriz W, Elger M, Nagata M, Kretzler M, Uiker S, Koeppen-Hageman I, et al. The role of podocytes in the development of glomerular sclerosis. Kidney Int 1994; 45: 64-72.
7. Takazakura E, Sawabu N, Handa A. Intrarenal vascular changes with age and disease. Kidney Int 1972; 2: 224-30. [CrossRef]
8. Rowe J, Andres R, Tobin J, Norris AH, Shock NW. The effect of age on creatinine clearance in men: A cross sectional and longitudinal study. J Gerontol 1976; 31: 155-63. [CrossRef]
9. Jeffrey BH, Joseph GO, Mary T, Stephanie S, Kevin PH, Sanjay A. Hazzard's Geriatric Medicine and Gerontology. 6th ed. USA: McGraw-Hill; 2009.
10. Davies D, Shock N. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. J Clin Invest 1950; 29: 496-507. [CrossRef]
11. Porter LE, Hollenberg NK. Obesity, salt intake, and renal perfusion in healthy humans. Hypertension 1998; 32: 144-8. [CrossRef]
12. Rowe J, Andres R. Tobin J. Age adjusted standards for creatinine clearance. Ann Intern Med 1976; 84: 567-9. [CrossRef]
13. Gral T, Young M. Measured versus estimated creatinine clearance in the elderly as an index of renal function. J Am Geriatr Soc 1980; 28: 492-6. [CrossRef]
14. Howard MF, Kenneth R, John BY. Brocklehurst's Textbook of Geriatric Medicine and Gerontology. 8th. Ed. Philadelphia: Elsevier; 2015.
15. Goldman L, Ausiello DA. Cecil Internal Medicine. 23th ed. Philadelphia: Saunders Elsevier; 2008.
16. Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41. [CrossRef]
17. Miller M, Gold GC, Friedlander DA. Physiological changes of aging affecting salt and water balance. Rev Clin Gerontol 1991; 1: 215-30. [CrossRef]
18. Miller M, Morley JE, Rubenstein LZ. Hyponatremia in a nursing home population. J Am Geriatr Soc 1995; 43: 1410-3. [CrossRef]
19. Raman A, Schoeller DA, Subar AF, Troiano RP, Schatzkin A, Harris T, et al. Water turnover in 458 American adults 40–79 yr of age. Am J Physiol Renal Physiol 2004; 286: F394.
20. Crowe M, Forsling M, Rolls B. Altered water excretion in healthy elderly man. Age Ageing 1987; 16: 285-93. [CrossRef]
21. Epstein M, Hollenberg N. Age as a determinant of renal sodium conservation in normal man. J Lab Clin Med 1976: 411-7.
22. Macias Nunez J, Garcia Islesias C, Bonda Roman A. Renal handling of sodium in old people: A functional study. Age Ageing 1978; 7: 178-81. [CrossRef]
23. Or K, Richards A, Espiner EA. Effect of low dose infusions of atrial natriuretic peptide in healthy elderly males: Evidence for a postreceptor defect. J Clin Endocrinol Metab 1993; 76: 1271-4. [CrossRef]
24. Sonnenblick M, Algur N. Hypernatremia in acutely ill elderly patients: Role of impaired arginine-vasopressin secretion. Miner Electrolyte Metab 1993; 19: 32-5.
25. Booker JA. Severe symptomatic hyponatremia in elderly outpatients: The role of thiazide therapy and stress. J Am Geriatr Soc 1984; 32: 108-13. [CrossRef]
26. Allen TH, Anderson EC, Langham WH. Total body potassium and gross body composition in relation to age. J Gerontol 1960; 15: 348-57. [CrossRef]
27. Walmsley RN, White GH, Cain M. Hyperkalemia in the elderly. Clin Chem 1984; 30: 1409-12.
28. Altun B. Kidney and aging. Turkish Journal of Geriatrics 1998; 1: 68-71.
29. Ambrecht HJ, Forte LR. Halloran BP. Effect of age and dietary calcium on renal 25 (OH)D metabolism, serum 1,25 (OH)D, and PTH. Am J Physiol 1984; 246: 266-70.
30. Ambrecht HJ, Gross CJ, Zenser TV. Effect of dietary calcium and phosphorus restriction on calcium and phosphorus balance in young and old rats. Arch Biochem Biophys 1981; 210: 179-85. [CrossRef]
31. Haas M, Spargo BH, Wit EJ, Meehan SM. Etiologies and outcome of acute renal insufficiency in older adults: a renal biopsy study of 259 cases. Am J Kidney Dis 2000; 35: 433-7. [CrossRef]
32. Pascual J, Liaño F, Ortuño J. The elderly patient with acute renal failure. J Am Soc Nephrol 1995; 6: 144-53.
33. DuBose TD, Warnock DG, Mehta RL, Bonventre JV, Hammerman MR, Molitoris BA, et al. Acute renal in the 21st century: Recommendations for management and outcomes assessment. Am J Kidney Dis 1997; 29: 793-9. [CrossRef]
34. Smets HL, De Haes JF, De Swaef A, Jorens PG, Verpooten GA. Exposure of the elderly to potential nephrotoxic drug combinations in Belgium. Pharmacoepidemiol Drug Saf 2008; 17: 1014-9. [CrossRef]
35. Baraldi A, Ballestri M, Rapanà R, Lucchi L, Borella P, Leonelli M, et al. Acute renal failure of medical type in an elderly population. Nephrol Dial Transplant 1998; 13: 25-9. [CrossRef]
36. Tan J, Afzal I, Yeadon A, Bird N, Gouldesbrough D, Akbani H. Spontaneous cholesterol embolisation causing acute renal failure. Clin Exp Nephrol 2007; 11: 235-7. [CrossRef]
37. Macias-Nunez JF, López-Novoa JM, Martínez-Maldonado M. Acute renal failure in the aged. Semin Nephrol 1996; 16: 330-8.
38. Mandal AK, Baig M, Koutoubi Z. Management of acute renal failure in the elderly. Treatment options. Drugs Aging 1996; 9: 226-50. [CrossRef]
39. Massry SG, Glassock RJ. Textbook of Nephrology. 3rd ed. Baltimore: Williams and Wilkins; 1995.
40. Donadio JV Jr. Treatment and clinical outcome of glomerulonephritis in the elderly. Contrib Nephrol 1993; 105: 49-57. [CrossRef]
41. Davison AM, Johnston PA. Idiopathic glomerulonephritis in the elderly. Contrib Nephrol 1993; 105: 38-48. [CrossRef]
42. Cameron JS. Nephrotic syndrome in the elderly. Semin Nephrol 1996; 16: 319-29.
43. Greco BA, Breyer JA. Natural history of renal artery stenosis. Semin Nephrol 1996; 16: 2-11.
44. Zucchelli P, Zuccala A. Ischemic nephropathy in the elderly. Contrib Nephrol 1993; 105: 13-24. [CrossRef]
45. Jennette JC, Olson JL, Schwartz MM, Silva FG. Heptinstall's Pathology of the kidney. 6th ed. Philadelphia: Lippincitt Williams and Wilkins, 2007.
46. Cozzolino M, Gallieni M, Brancaccio D, Arcidiacono T, Bianchi G, Vezzoli G. Vitamin D retains an important role in pathogenesis and management of secondary hyperparathyroidism in chronic renal failure. J Nephrol 2006; 19: 566-77.
47. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kid Dis 2003; 42: S1-201.
48. National Kidney Foundation. K/DOQI Clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. Am J Kidney Dis. 2006; 47: S11-145.
49. Süleymanlar G, Ateş K, Seyahi N. Türkiye'de nefroloji, diyaliz ve transplantasyon registry 2014. T.C. Sağlık Bakanlığı ve Türk Nefroloji Derneği ortak raporu. Ankara, 2015.