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12 The Elderly Kidney

Francesco M. Drudi

12.1 Introduction

It is estimated that after the age of 30 years, GFR progressively declines at an average rate of 8 mL/min/1.73 m/decade [1]. Structural and functional changes affect all components of the kidney. These variations tend to reduce renal functional reserve. Many factors affect kidney changes in the elderly: genetic factors, genomic alterations, oxidative stress, nutrition, drugs, and infections. In addition, elderly patients are frequently affected by clinical conditions such as arterial hypertension, diabetes mellitus, and cardiovascular diseases that can play an additive role in age-related changes, tending to amplify these abnormalities [1].

12.2 Structural Changes

In the elderly, a progressive reduction of renal mass is described; the weight of the kidneys is reduced from about 250–270 g in the young adult to 180–200 g in the eighth decade of life with preferential loss of cortical parenchyma, with relative spare of the medullary one.

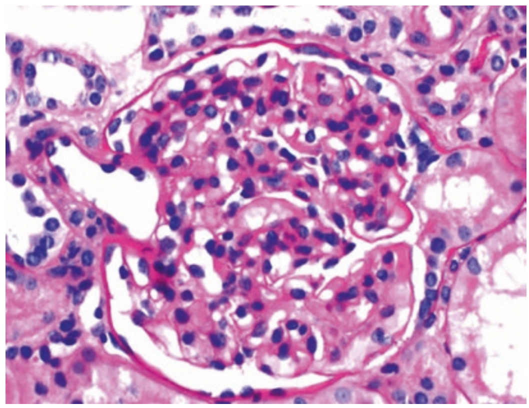

Fig. 12.1 Focal and segmental glomerulosclerosis

On a microscopic level, this atrophy coincides with a reduction in the number of functioning nephrons [2].

In particular glomeruli undergo focal and segmental glomerulosclerosis, thickening of the glomerular basement membrane, and compensatory hypertrophy of the surviving glomeruli [3] (Fig. 12.1).

The tubules encounter dilatation, atrophy, and diverticula, which in turn are possible sites of bacterial colonization and precursors of parenchymal cysts [4].

Interstitium undergoes fibrosis with “patchy” inflammation.

About vessels, we can see hyaline arteriosclerosis (especially in the presence of diabetes), hyperplastic sclerosis of arterioles (especially in

F. M. Drudi (✉)
Department of Radiological Sciences, University La Sapienza of Rome, Rome, Italy
e-mail: Francescom.Drudi@uniroma1.it

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the presence of malignant hypertension), and middle-intimal hypertrophy (especially in the presence of hypertension) [5].

12.3 Functional Changes

In the elderly there is a progressive reduction in creatinine clearance of about 50% between 30 and 80 years, as well as a reduction in glomerular filtration rate (VGF) [6].

A problem of advanced age concerns the evaluation of renal function, unreliable on the basis of widely available and economic indicators, valid in young and adult age, such as creatininemia [6].

The renal function in humans can be evaluated by a variety of equations, one of the most used of which is the Cockcroft-Gault equation.

The parameters used in this formula are age, sex, body weight, serum creatinine levels (Scr), and constant values [7]:

$$\frac{\text{COCKROFT GAULT -EQUATION}}{\left[(140 - \text{age}) \times \text{weight} / 72 \times \text{Scr}\right](\times 0.85 \text{if female})}$$

Unfortunately, predictive value of the Cockcroft-Gault formula is not optimal in the elderly patient (age >70 aa).

Serum creatinine levels depend on muscle mass that usually reduces with aging. Furthermore, patients with chronic renal insufficiency go on a hypoproteic diet.

Therefore, plasma creatinine levels may not be sensitive markers of actual renal function in chronic renal failure; in fact, many patients may have serum creatinine levels within the normal range even if they have a significant reduction in renal function [8].

As a consequence, for a more accurate evaluation of renal function, the clearance of creatinine with urine collection in 24 h is recommended [9].

Moreover, in the elderly, in addition to a reduction of the lean mass, there is often an increase in fat mass, which induces a pro-inflammatory state [10].

Oxidized LDLs are able to stimulate the production of inflammatory and fibrogenic cytokines, which are responsible for apoptosis of mesangial cells and for increase in the production of reactive O_2 species, creating a self-perpetuating mechanism.

This results in a higher production of matrix and collagen proteins as well as an increased apoptosis of endothelial cells.

In addition, oxidized LDLs increase the production of vasoactive substances such as endothelin and thromboxane and increase renin release from juxtaglomerular cells [10].

A reduction of vasodilating factors, such as NO (nitric oxide), has also been reported [10].

12.4 Ultrasound and Color Doppler Evaluation of Kidney in Elderly

Renal ultrasound in the elderly can provide information related to response to specific clinical questions or can be considered as an extension of the objective examination. The integration with anamnestic, objective, and laboratory data permit fast and reliable clinical, diagnostic, and therapeutic classification.

12.4.1 Ultrasound

Renal ultrasound (US) has become a routine investigation in kidney disease.

It is able to determine the number, location, size, and shape of kidneys.

Size of kidneys and parenchymal echogenicity are considered markers of renal function, so US can be considered useful to assess the presence and degree of renal failure (Figs. 12.2 and 12.3). US can show a reduction of the longitudinal diameter (15% between the third and the ninth decades of life) and a reduction of the volume (mainly due to loss of the parenchymal component) [2].

A renal longitudinal diameter of 9 cm and an average parenchymal thickness of 12 mm are considered within the lower limits of the standard; lower values are considered pathological. However, an accurate evaluation of ultrasound

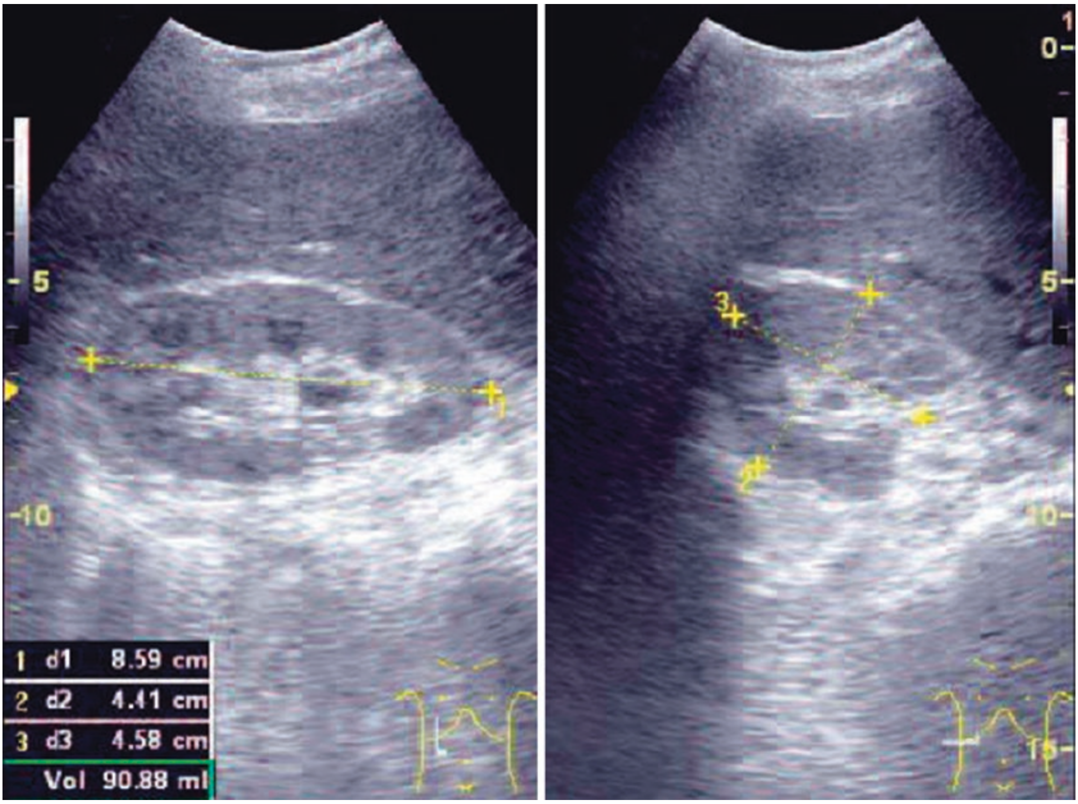


Fig. 12.2 Reduction of the longitudinal diameter and volume

Fig. 12.3 Change in parenchymal (cortical) echogenicity

information must provide for a "correction" for some constitutional parameters (age, sex, body weight, height, blood pressure, sex) [11].

A hiding effect on the reduction of renal size is the apparent normality of the latter in the presence of pathological conditions that increase renal size, as inflammatory processes, infiltration, or accumulation, which can hide a preexisting dimensional reduction; conversely, the latter can mask the increase in dimensional parameters when clinically expected (Fig. 12.4) [12].

Mancuso et al. measure renal diameters, volume, and cortical thickness in association with functional parameters (creatinine and creatinine clearance) in patients with varying degrees of chronic renal failure and in a population of control showing a correlation between size parameters seen with US and decline of GFR during chronic renal failure [11].

Beyond dimensional aspects, senile kidney shows frequent morphological-qualitative ultrasound changes. Cortical-medullary differentiation of the parenchyma is reduced with age and is evident only in about 1/3 of the elderly subjects (Fig. 12.2).

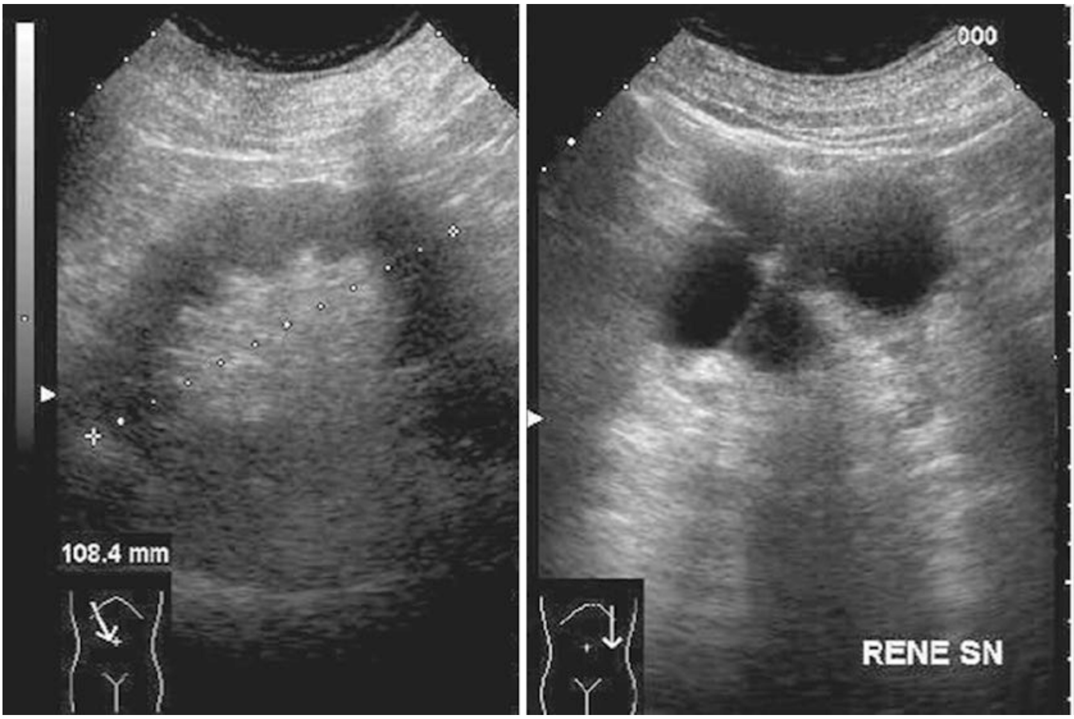


Fig. 12.4 Right kidney: normal size and parenchymal thickness. Left kidney: disappearance of parenchyma, represented exclusively by pyelocaliceal sacs

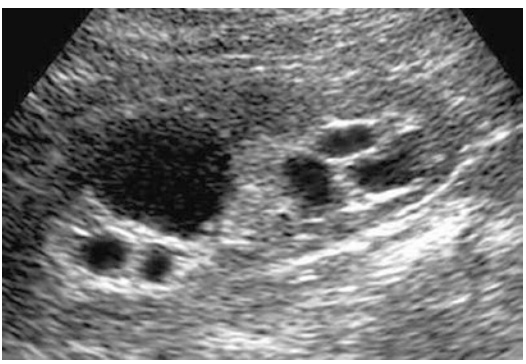


Fig. 12.5 Multiple cystic formations of variable sizes

The finding of cystic formations of variable sizes is frequent on parenchyma and renal sinus [12] (Fig. 12.5).

Moreover, there is frequent finding of a relative hypertrophy of the sinus component, with a reduced parenchyma-sinus ratio.

Increase in sinus share could morphologically compensate for parenchymal loss, so that the volumetric maintenance of the whole organ does not necessarily express the preservation of the functional renal mass, that is, the parenchymal mass; this, therefore, should be measured specifically, subtracting the sinus volume from the total renal volume.

Both volumes can be calculated through the simplified formula of the ellipsoid, i.e., from the product of the three main diameters of the kidney (longitudinal, transversal, and anterior-posterior) for 0.52 [13].

12.4.2 Color Doppler

Senile alterations are evaluable with ecocolor and ecoDoppler. In the elderly, distribution of color signals and expression of the renal vascular tissue appear more attenuated compared to the young or young-adult population, limited to intersegmental and interlobar districts [14] (Fig. 12.6).

Among the ecoDoppler parameters, the one considered most reproducible and less influenced by methodological factors is the **resistance**

index. It is higher in the elderly population; however, it is influenced by various physiological and pathological conditions both intra- and extrarenal, so its modifications or alterations, especially its increase, are not very specific. In elderly an upper limit of 0.70 is usually considered [15] (Figs. 12.7 and 12.8).

According to Tublin et al., a correct sampling must provide the measurement of at least 3/5 waves of dimensions overlapping in three different areas of each kidney; the final value of IR considered corresponds to the arithmetic mean of the values obtained [16]. However, a correct IR can be difficult to evaluate in some conditions such as tachycardia, bradycardia, arrhythmia, and presence of perirenal or subcapsular liquid collections [17].

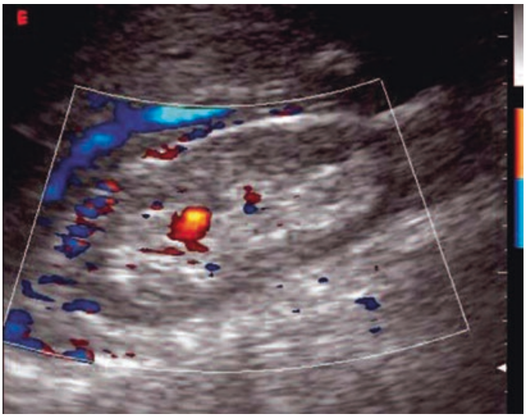


Fig. 12.6 Reduced vascular representation, due to scarcity of color signals (PRF 1 KHz). Using a lower PRF the increase in vascular signals would be affected by the appearance of artifactual motion signals, such as those already evident at the periphery of the kidney

12.5 Renal Disorders in the Elderly

Kidneys in elderly lose the ability to repair itself after a damage, the ability to react to any stress condition, the ability to react to hemodynamic alterations, and the ability to maintain body homeostasis (water, electrolytes, pH) because adaptation mechanisms are reduced.

So kidneys are more susceptible to nephrotoxic factors.

As life expectancy continues to improve worldwide, there is a rising prevalence of comorbidities and risk factors such as hypertension, diabetes, and cardiovascular disease [18]. Several diseases that afflict kidneys in young-adult population have more incidence or worse consequences in the elderly.

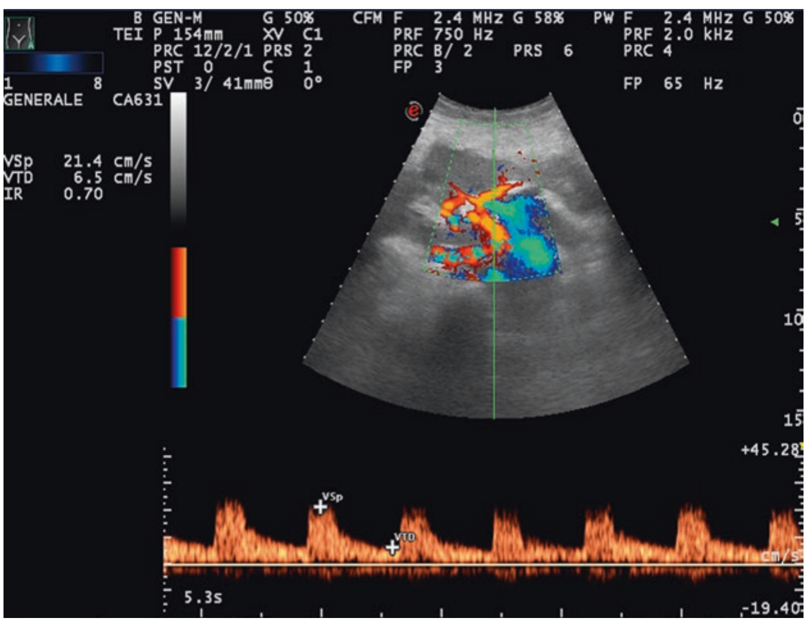


Fig. 12.7 IR = 0.70 in 65-year-old woman

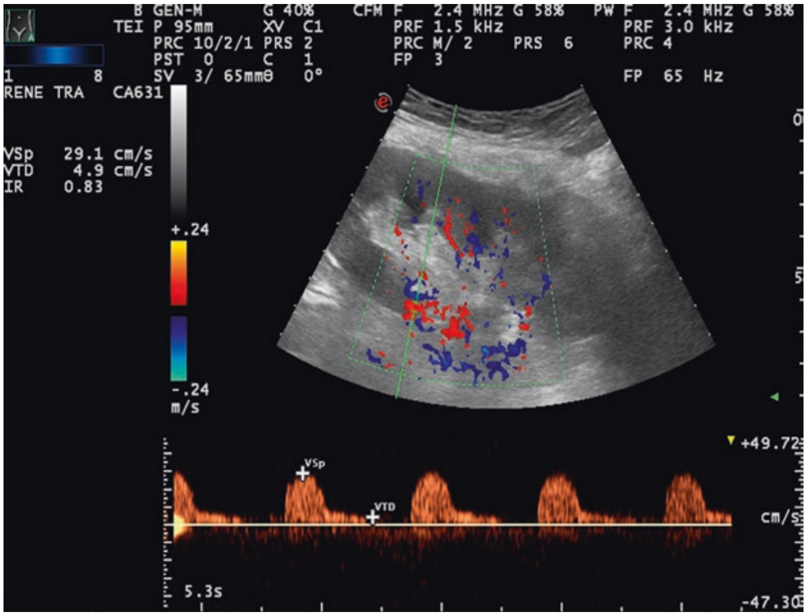


Fig. 12.8 IR = 0.83 in 70-year-old woman

12.5.1 Chronic Kidney Disease (CKD)

Chronic kidney disease (CKD) is a very common clinical problem in elderly patients and is associated with increased morbidity and mortality. CKD definitions are kidney damage evidenced by abnormal renal markers or a reduction of the absolute eGFR to less than 60 mL/min/1.73 m^2 for at least 3 months. Abnormal renal markers are proteinuria, abnormal radiology, abnormal cells in the urine, or renal pathology on biopsy. In addition, a history of renal transplantation is included in the definition [18].

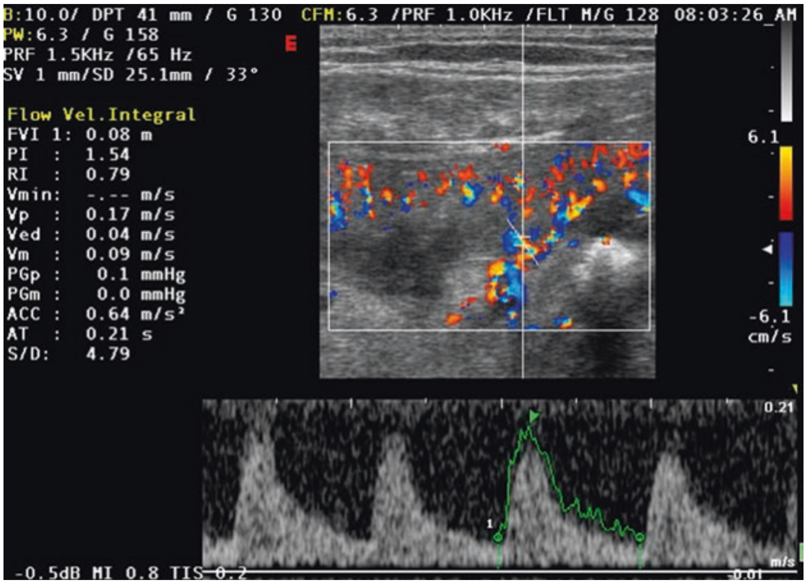
In the elderly, frequent etiopathogenic causes of chronic renal failure are nephrovascular pathologies. In uremic patients, in fact, cardiovascular events represent the largest cause of death, which is about 20 times greater than the general population. In these patients, cerebrovascular accidents appear ten times more frequently than in the general population. In particular, it has been reported that about 50% of patients starting hemodialysis have coronaropathies on atherosclerotic basis; 80% of these patients have dyslipidemia [19]. Atherosclerosis is often present in the uremic patient in a very advanced phase. In fact, it has been shown that the mean intimal thickness of the carotid and femoral arteries, as a marker of atherosclerosis, is higher in patients on hemodialysis compared to healthy controls of the same age and sex [20]. Arterial hypertension, obesity, and diabetes mellitus are also common causes of chronic renal failure in the elderly patient [18].

12.5.1.1 US/Color Doppler

US shows increased echogenicity of the cortex, decreased renal size, and cortical thinning, findings rather frequent in the kidney of the elderly and therefore nonspecific [12].

IR value can be considered a marker of renal damage progression paying attention to possible concomitant confounding factors (renal compression, Valsalva maneuver, cardiac rhythm abnormalities, various extrarenal causes of altered vascular elasticity, etc.) [17]. High IR value $\geq$0.80 (Fig. 12.8) represents a point of no return in the diagnosis of IRC, being associated with a reduced probability of improvement of renal function after percutaneous transluminal angioplasty (PTA). In transplanted kidney it is predictive of a reduced graft survival. A correlation between IR >0.70 and percentage increase in serum creatinine values has been reported, so an

Fig. 12.9 IR increase in chronic kidney disease



IR value >0.70 (Fig. 12.9) may be considered an independent risk factor for worsening renal function in the IRC [17].

12.5.2 Occult Renal Insufficiency (ORI)

It is characterized by normal creatinine and reduced glomerular filtration rate (VFG), frequent in the elderly population and associated with greater risk of adverse pharmacological events.

A ClCr <60 mL/min with creatinine <1.1 mg/dL was identified as ORI.

In clinical practice, the 24-h creatinine clearance (ClCr24h) or the predictive equations of VFG (EP) are used to evaluate renal function. The main EPs are the Cockcroft-Gault equation, the modification of diet in renal disease (MDRD), and the CKD-EPI (chronic kidney disease epidemiology collaboration).

In the hospitalized elderly the prevalence of ORI (ClCr <60 mL/m) was 50.9% [21].

Among the EPs, the estimate of VFG using the Cockcroft-Gault formula seems to provide results that are more similar to those of ClCr24h [21].

12.5.3 Diabetic Nephropathy

Diabetes type 2 has a high incidence among the elderly. Forty percent of type 2 diabetics are at risk of chronic renal disease [22].

Diabetic nephropathy consists of sclerosis and glomerular fibrosis caused by metabolic and hemodynamic changes in diabetes mellitus: thickening of glomerular basement membrane, and capillary and tubular basement membrane thickening. Other glomerular changes include loss of endothelial fenestrations, mesangial matrix expansion, and loss of podocytes [22]. The exudative lesions result from subendothelial deposits of plasma proteins, which form periodic acid-Schiff-positive and electron-dense deposits and accumulate in small arterial branches, arterioles, and glomerular capillaries as well as microaneurysms. Similar subepithelial deposits are seen in Bowman's capsule (capsular drop lesion) and proximal renal tubules [22] (Fig. 12.10).

Diabetic nephropathy manifests as a slowly progressive albuminuria, with a worsening of hypertension and renal failure. Diagnosis is based on anamnesis, physical examination, urinalysis, and urinary albumin/creatinine ratio. Treatment consists of strict glycemic control

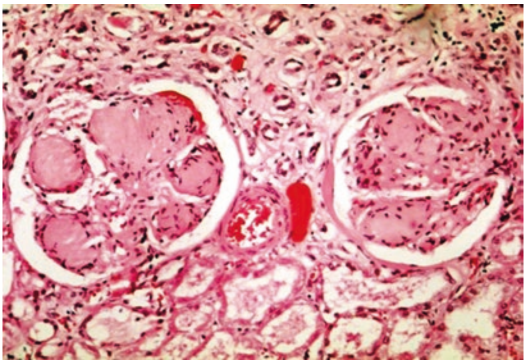


Fig. 12.10 Diabetic glomerulopathy

(using ACE inhibitors and/or angiotensin II receptor inhibitors) and controlling of blood pressure and lipids [22].

Patients are routinely tested for urine detection of proteinuria; if present, the test for microalbuminuria is not necessary because the patient already has a suggestive macroalbuminuria for diabetic nephropathy. In patients without proteinuria, the albumin/creatinine ratio should be measured on a urine sample of the first morning urination. A creatinine ratio ≥0.03 mg/mg (≥30 mg/g) indicates microalbuminuria if it is present in at least two of the three measurements performed within 3–6 months and if it cannot be explained by the presence of infections or exercise [22].

12.5.3.1 US/Color Doppler

IRs are useful indicators of the presence of nephropathy in patients with type 2 diabetes mellitus, even in the absence of microalbuminuria: increased IR represents a risk factor for the development of albuminuria and higher IR is also reported in the presence of macroalbuminuria, even after adjusting for GFR values. In type 2 diabetic patients without microalbuminuria, the increase in IR is predictive of renal involvement.

12.5.4 Acute Renal Failure

Acute renal failure (ARF) is a common problem in older adults. As compared to younger adults, elderly have a greater prevalence of ischemic ARF. Relevant structural and functional changes in the aging kidney predispose to ARF: arteriosclerotic lesions at the level of interlobular and arcuate arteries that causes increase in vascular resistances; decreased ability to retain sodium, due to decreased reabsorptive tubular capacity and impaired aldosterone secretion; tendency to dehydration, due to decreased urinary concentrating ability and deficit in thirst; greater use of drugs that alter intrarenal hemodynamics, such as ACE inhibitors and NSAID; and higher incidence of cardiovascular comorbidity [23].

Obstructive ARF is also more frequent in older people, as well as some intrinsic causes, such as acute cryoglobulinemia, vasculitis, acute interstitial nephritis, acute tubular necrosis, light-chain cast nephropathy, and vascular diseases [23].

Diagnosis is based on the monitoring of creatinine, associated or not with urine production [24].

12.5.4.1 US/Color Doppler

Ultrasound of the urinary tract within 24 h is indicated in all patients in whom the cause of IRA cannot be identified and in those at risk of urinary tract obstruction [24].

In fact urinary tests, normally used in clinical practice, often result to be not useful in the differential diagnosis between the functional (prerenal) and the organic (intrarenal) form due to the presence of confounding factors (use of diuretics, antihypertensive drugs, urinary tract infections, sepsis, etc.) [17].

Intrarenal IRs may be useful for differential diagnosis: mean IR values are significantly higher in patients with organic IRA than those with functional IRA (0.74 ± 0.13 vs. 0.67 ± 0.09, $p < 0.0$) [17] (Figs. 12.11 and 12.12).

Finally, it has been demonstrated that renal IRs predict the onset of IRA in the immediate postoperative period in patients undergoing cardiac surgery with discrete sensitivity (85%) and high specificity (94%) [17].

12.5.5 Vasculitis

Primary and secondary glomerulonephritis, renal vasculitis, and interstitial nephropathies are com-

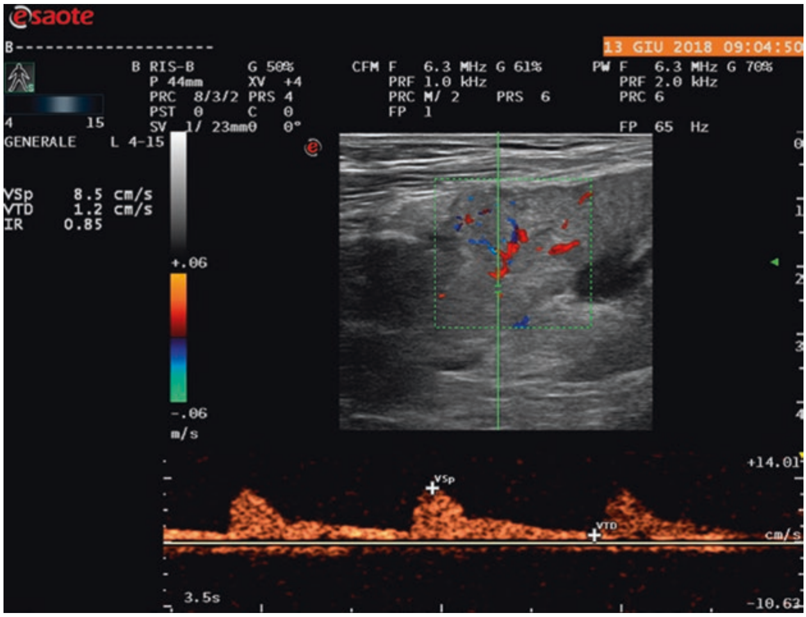


Fig. 12.11 Patients with organic IRA

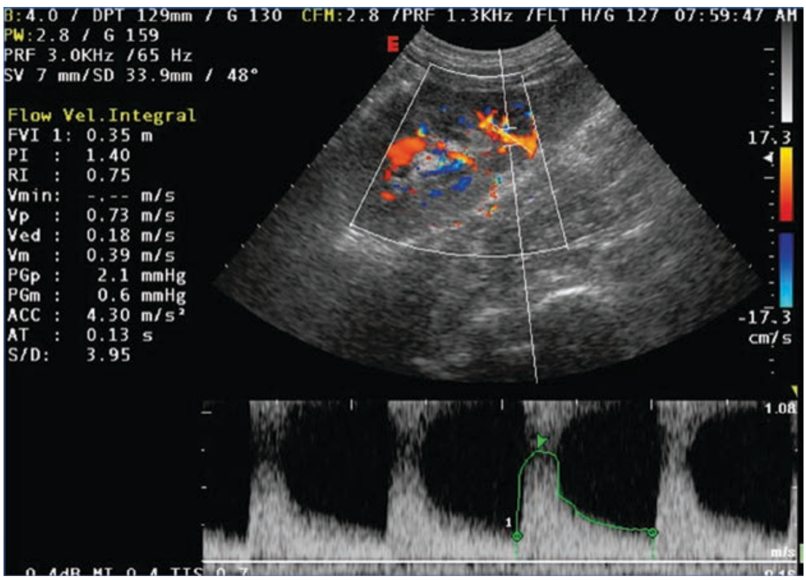


Fig. 12.12 Patients with functional IRA

mon groups of diseases among the elderly. The gold standard is the biopsy. For acute pyelonephritis, instead, the suspicion is placed on a clinical-laboratory basis, but the assessment is based on radiological criteria [25].

12.5.5.1 US/Color Doppler

Patients with vasculitis have higher values of IR (mean IR 0.82 ± 0.05) than those suffering from a pathological process limited to glomeruli (mean IR 0.58 ± 0.05). There is also an anomalous morphology of the Doppler wave in which there is a reduction of the diastolic component rather than the systolic [17].

In patients with lupus nephritis, the detection of IR >0.70 represents an important risk factor of chronicity and correlates with higher creatinine values compared to patients with normal resistance indexes, which appear to have a better renal prognosis [17].

12.5.6 Acute Obstructive Uropathy

Obstructive uropathy is the blockage of urinary flow, which can affect one or both kidneys. Obstructive uropathy becomes more prevalent with increasing age so the diagnosis and management of obstructive uropathy are particularly relevant to the geriatric population [25].

If only one kidney is affected, urinary output may be unchanged and serum creatinine can be normal. When kidney function is affected, this is termed obstructive nephropathy [25].

Main causes of obstructive renal disease in the elderly are benign prostatic hyperplasia and neurological bladder [26]; other common causes are urolithiasis, intrinsic or extrinsic ureteral obstruction, severe bladder ptosis (prolapse and tumors of the uterus, appendages, and vagina), and abdominal aortic aneurysm.

Acute or chronic obstruction of the urinary tract determines renal ischemia, tubular atrophy, and interstitial and glomerular fibrosis, worsening degenerative processes that already afflict senile kidney.

12.5.6.1 US/Color Doppler

Ultrasound, in the suspicion of obstructive nephropathy, should explore kidney, ureters, retroperitoneal space, and pelvic excavation.

It can differentiate acute and chronic obstructive nephropathies: in the first case, kidney has normal or increased dimensions and preserved thickness of parenchyma with accentuated echogenicity; in the second case kidney is small with thinning of parenchyma and hyperechogenic structure.

A mean IR value of 0.69 was reported in obstructed kidneys, while mean IR values of 0.67 and 0.59 were found, respectively, in acutely obstructed kidneys and in unobstructed kidneys with ΔIR (the difference between the mean value of the IR sampled in the two kidneys) significantly high, equal to 0.076. ΔIR has a predictive value of obstruction with 94% sensitivity and 95% specificity.

An IR value >0.70 is correlated with acute renal obstruction and precedes ectasia pyelocaliceal.

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