

KIDNEY DAMAGE IN AUTOIMMUNE DISEASES OŠTEĆENJA BUBREGA U AUTOIMUNIM BOLESTIMA

Manole Cojocar¹, Inimioara Mihaela Cojocar²,
Isabela Silosi³, Camelia Doina Vrabie⁴

¹»Titu Maiorescu« University, Faculty of Medicine, Department of Physiology,
Center for Rheumatic Diseases, Bucharest, Romania

²»Carol Davila« University of Medicine and Pharmacy,
Clinic of Neurology, Colentina Clinical Hospital, Bucharest, Romania

³University of Medicine and Pharmacy, Department of Immunology, Craiova, Romania

⁴»Carol Davila« University of Medicine and Pharmacy, Clinical Hospital of Emergency »Sfantul Ioan«,
»Victor Babes« National Institute for Pathology and Biomedical Sciences, Bucharest, Romania

Summary: Renal involvement in autoimmunity has many facets. Glomerular, tubular and vascular structures are targeted and damaged as a consequence of autoimmune processes. Immunologically mediated kidney diseases represent the third most common cause of end-stage renal failure (after diabetic and hypertensive nephropathies). Appropriate evaluation of patients with immune-mediated kidney diseases requires a meticulous history and physical examination, with particular attention to the urinalysis, tests of renal function and often renal biopsy. The thorough clinician should personally review microscopic urinalysis in any case in which there is a reasonable index of suspicion of immune-mediated renal disease. In this article we propose to highlight recent developments, with particular reference to renal autoimmunity. Systemic lupus erythematosus affects many parts of the body: primarily the skin and joints, but also the kidneys. Goodpasture's syndrome involves an autoantibody that specifically targets the kidneys and the lungs. IgA nephropathy is a form of glomerular disease that results when immunoglobulin A (IgA) forms deposits in the glomeruli, where it creates inflammation. Future research could look for how the disease occurs, and how to easily test for its presence so that early treatment could be started.

Keywords: kidney damage, autoimmune diseases, pathophysiology

Kratak sadržaj: Bubrezi na više načina učestvuju u autoimunitetu. Usled autoimunih procesa, glomerularne, tubularne i vaskularne strukture bivaju prepoznate i oštećene. Imunološki posredovana bubrežna oboljenja predstavljaju treći najčešći uzrok otkazivanja bubrega (posle dijabetičkih i hipertenzivnih nefropatija). Pravilna evaluacija pacijenata sa imunološki posredovanim bubrežnim bolestima zahteva preciznu anamnezu i fizički pregled, uz pridavanje naročite pažnje analizi urina, testovima renalne funkcije i često renalnoj biopsiji. Temeljni kliničar bi trebalo lično da pregleda rezultate mikroskopske analize urina u svakom slučaju gde postoji osnovana sumnja da se radi o imunološki posredovanoj bolesti. U ovom radu pokušali smo da predstavimo najnovija dostignuća, s posebnim osvrtom na renalni autoimunitet. Sistemske lupus eritematodes zahvata mnoge delove tela: pre svega kožu i zglobove, ali i bubrege i pluća. IgA nefropatija je oblik glomerularne bolesti koja nastaje kada imunoglobulin A (IgA) stvori depozite u glomerulima, gde izaziva inflamaciju. Buduća istraživanja mogla bi otkriti kako bolest nastaje i na koji način bi se testiranjem lako moglo utvrditi njeno prisustvo da bi se blagovremeno počelo sa tretmanom.

Ključne reči: oštećenje bubrega, autoimune bolesti, patofiziologija

Introduction

Autoimmune diseases may be systemic and affect many parts of the body, or they may affect only specific organs or regions. The main causes of renal injury are based on immunologic reactions (initiated by immune complexes or immune cells), tissue

Address for correspondence:

Manole Cojocar
Str. Thomas Masaryk No. 5 Sector 2 Postal Code 020983
Bucharest, Romania
e-mail: manole_cojocar@yahoo.com

hypoxia and ischemia, exogenic agents like drugs, endogeneous substances like glucose or paraproteins and other, and genetic defects (1).

Inflammatory renal disease in the context of autoimmunity occurs because the kidney is targeted by effector responses. Once antibodies are deposited, their exposed Fc (fragment crystalline) regions activate and recruit inflammatory cells, and initiate complement activation. This process leads to further cellular infiltration, and secretion of inflammatory mediators by both infiltrating and endogenous cells. Infiltrating cells, which include neutrophils, T-cells and macrophages, and platelets also secrete soluble mediators and directly interact with renal cells and each other to perpetuate the disease process (2, 3).

Immune complexes can be deposited in the mesangium (as in IgA nephropathy, Henoch Schonlein purpura, lupus nephritis class II, postinfectious GN), in subendothelial (lupus nephritis class III, membranoproliferative GN), or subepithelial area (idiopathic membranous nephropathy or class V lupus nephritis, postinfectious GN), or along GBM (as in anti-GBM disease). A strong inflammatory reaction occurs only when circulating inflammatory cells can be activated by contact with immunoglobulins or soluble products released by intrinsic renal cells (4).

In most cases, the autoantigens are non-renal and become renal targets because of the physiological properties of the high flow, high-pressure perm-selective filtration function of the glomerulus. Circulating autoantigens can deposit in glomeruli as part of circulating immune complexes (5).

When the body's immune system functions properly, it creates protein-like substances called antibodies and immunoglobulins to protect the body against invading organisms. In an autoimmune disease, the immune system creates autoantibodies, which are antibodies or immunoglobulins that attack the body itself (6).

In most cases, the autoantigens are non-renal and become renal targets because of the physiological properties of the high flow, high-pressure perm-selective filtration function of the glomerulus. Circulating autoantigens can deposit in glomeruli as part of circulating immune complexes or become a »planted« target antigen by their physico-chemical properties that predispose to their glomerular fixation. A potentially unique model of deposition of a non-renal antigen in the kidney is seen in antineutrophil cytoplasmic antibody (ANCA) associated small vessel vasculitis, where target autoantigens originating in neutrophil cytoplasmic granules and expressed in the cell membrane (including proteinase-3 [PR3] and myeloperoxidase [MPO]) are targeted by ANCA. These ANCA-activated neutrophils have altered flow characteristics which results in their lodging in small vessels, particularly glomeruli, leading to renal injury (7).

Within the kidney, the local response of resident cells plays an important role in determining the severity of inflammation. If severe and/or unlimited, these events may lead to fibrosis and organ failure (8).

As mentioned, one can envision several ways by which the kidneys become involved. In addition, the kidneys may become affected by antibody-mediated mechanisms where the autoantigen resides outside the kidney. Deposition of resulting immune-complexes within the kidneys subsequently triggers tissue damaging events (e.g. lupus nephritis). Third, antigen and antibodies are neither derived nor deposited within the kidneys. However, the interaction of antibodies with the antigens, or with antigen-bearing cells, causes the disease (e.g. ANCA vasculitis and glomerulonephritis) (9).

Membranoproliferative glomerulonephritis

Membranoproliferative glomerulonephritis is a form of glomerulonephritis that is classified as an autoimmune disease. Membranoproliferative glomerulonephritis (MPGN) is a rare condition sometimes called mesangiocapillary glomerulonephritis. Besides the presence of pathologic immunoreactants in glomerular sites, the immune-mediated nature of this disease is suggested by the high frequency of persistent hypocomplementemia. It is of interest that both congenital complement deficiencies (e.g. deficiency of complement component C3) and sustained hypocomplementemia induced by nephritic factor autoantibodies or circulating immune complexes have been associated with MPGN. Antibodies to some unknown protein, called an antigen, get trapped in the filtering bed of the kidney, called the glomerulus. Once there, this antigen sets up a reaction in the normal cells that activates the so-called »killer cells«. These cells are very destructive and result in walling off the antigen. This produces a scar, which destroys normal architecture of the glomerulus (10).

Goodpasture's syndrome

Anti-glomerular basement membrane (anti-GBM) disease is the best-defined renal organ-specific autoimmune disease. The disease is strongly associated with autoantibody formation to a specific target found in the glomerular and alveolar basement membranes, and is characterized by a rapidly progressive glomerulonephritis (RPGN) which is often associated with pulmonary hemorrhage, though either may occur alone. Goodpasture's syndrome involves an autoantibody that specifically targets the kidneys and the lungs. But lung damage in Goodpasture's syndrome is usually superficial compared with progressive and permanent damage to the kidneys. Diagnosis is based on the demon-

stration of anti-GBM antibodies, either in the circulation or fixed to basement membrane of affected organs on biopsy. Probably the best test for anti-GBM is the renal biopsy with the detection of linear IgG depositions along the GBM. However, most patients also have circulating anti-GBM antibodies in their plasma detected by enzyme-linked immunosorbent assay (ELISA) or Western blotting. The majority of these antibodies are of the IgG1 subtype, with only few IgG4 antibodies. Very rarely, patients have no detectable anti-GBM IgG, but IgA or IgM antibodies instead. Anti-glomerular basement membrane (GBM) antibodies may be present and up to 80 percent of patients show the presence of ANCA with or without an accompanying vasculitis. A pathogenic role of these antibodies was demonstrated by elution and transfer to primates. The term »Goodpasture's syndrome« was then used for the triad of lung hemorrhage, renal failure and anti-GBM antibodies. Now some authors prefer the term »Goodpasture's disease« for glomerulonephritis caused by antibodies directed against the $\alpha 3$ -chain of type IV collagen, with or without lung hemorrhage. Rapidly progressive glomerulonephritis (RPGN) is a heterogeneous group of disorders characterized by a rapidly progressive disease course that can lead to kidney failure in only a few weeks or few months. These syndromes are characterized by focal necrotizing glomerulonephritis and crescent formation within the kidney's Bowman capsules (11, 12).

Systemic lupus erythematosus

Renal involvement affects most patients with systemic lupus erythematosus (SLE). Nephritis is a major cause of morbidity and mortality and accounts for a large proportion of all hospital admissions in the lupus population.

Systemic lupus erythematosus (SLE) is the prototypic systemic autoimmune disease with widespread clinical manifestations. Systemic lupus erythematosus (SLE) affects many parts of the body: primarily the skin and joints, but also the kidneys. SLE can cause the body to produce antibodies directed against the kidney membranes. The prevalence of renal involvement depends strongly on the definition. Almost 100% of the patients will have renal manifestation if immunoglobulin deposition is the criterion, whereas the percentage is approximately 50% if proteinuria is applied. Renal involvement is one of the most serious complications, since nephritis may progress into end stage renal disease (ESRD) and is associated with increased mortality. Changing classifications were applied over past decades. More recently, the ISN/RPS 2003 classification was introduced. The most severe lesions are found in Class IV, with diffuse proliferative GN. Lupus nephritis is the name given to the kidney disease caused by SLE, and it occurs when autoantibodies form or are deposited in the

glomeruli, causing inflammation. Ultimately, the inflammation may create scars that keep the kidneys from functioning properly. SLE can cause the body to produce antibodies directed against the kidney membranes. Normally, the filtering membranes do not permit albumin and other blood proteins to be lost in the urine. However, when systemic lupus attacks the kidney, the filtering membranes are disrupted, resulting in the finding of protein in the urine (3).

Several different mechanisms appear to be involved in the pathogenesis of lupus nephritis, resulting in a wide spectrum of renal lesions. DNA and anti-DNA antibodies are known to be concentrated in glomerular deposits in the subendothelial location and are likely to play a central role in the pathogenesis of proliferative lupus nephritis. Deposition of immune complexes from the circulation into the kidney and in situ complex formation may both be important in the pathogenesis of proliferative lupus nephritis; however, only a subset of immune complexes appears to be nephritogenic. Unfortunately, there are few insights into the pathogenesis of the lupus membranous nephropathy with its characteristic epimembranous immune deposits. Although T cells are almost certainly involved in autoantibody production, it is unknown whether they have a direct role in the pathogenesis of lupus nephritis. Several autoantibodies are generated in lupus patients (antinuclear antibodies (ANAs) and anti-double stranded DNA antibodies (dsDNA) included in diagnostic criteria). Not all of these antibodies seem to mediate renal damage or indicate renal involvement. For nephrologists, antibodies to anti-C1q and to nucleosomes are of particular interest. It is suggested that complexes of nucleosomes and the resulting antinucleosome antibodies bind to heparan sulphate-rich glomerular structures and induce the inflammatory reactions leading to glomerulonephritis (13, 14).

IgA nephropathy

As many as 50% of people with IgA nephropathy do not develop serious disease. IgA nephropathy is a form of glomerulonephritis. Damage is caused in the kidney by the abnormal buildup of a protein (IgA). Research suggests that this is due to an autoimmune disorder (involving the body's immune system). IgA nephropathy is a form of glomerular disease that results when IgA forms deposits in the glomeruli, where it creates inflammation. IgA nephropathy was not recognized as a cause of glomerular disease until the late 1960s, when sophisticated biopsy techniques were developed that could identify IgA deposits in kidney tissue. Glomerular diseases (glomerulonephritis) are kidney disorders that affect the blood supply of the renal tubules. This results in the loss of complete nephrons, which leads to increased levels of blood urea and the uremic syndrome.

The most common type of glomerulonephritis is IgA nephropathy in which deposits of IgA interfere with kidney function. The most common symptom of IgA nephropathy is blood in the urine, but it is often a silent disease that may go undetected for many years. It appears to affect men more than women. Studies are trying to discover how to best prevent the disease from becoming kidney failure, or even how to reverse the disease's effects (2).

ANCA-associated vasculitis and glomerulonephritis

The most frequent subgroup of primary systemic vasculitis is that associated with circulating autoantibodies to neutrophil cytoplasmic antigens (ANCA), with involvement of microscopic blood vessels without immune deposits in the vessel walls, »pauci-immune micro-vasculitis«. They are also the most frequent autoimmune diseases that affect the kidneys in a rapidly progressive manner. Glomerulonephritis, with fibrinoid necrosis and crescent formation, is common (3) (Table I).

Table I Renal involvement in systemic vasculitis.

- Vasculitis with glomerular involvement includes microscopic polyangiitis, Wegener's granulomatosis and necrotizing crescent glomerulonephritis (renal-limited vasculitis).
- Associated with anti-neutrophil cytoplasmic antibodies (ANCA).
- Rapidly progressive glomerulonephritis is common.

ANCA are autoantibodies that are directed to neutrophil and monocyte constituents. ANCA are found in sera of patients with Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS) or a renal-limited form presenting with necrotizing crescentic glomerulonephritis (ANCA-GN) (4).

Scleroderma (systemic sclerosis)

Renal disease occurs in the diffuse form of systemic sclerosis and is a major cause of morbidity and mortality in these patients. Renal disease in scleroderma covers a spectrum of manifestations, with a slowly progressive form of chronic renal disease at the one extreme and acute scleroderma renal crisis at the other. Rapid progression of skin disease has also been associated with an increased frequency of renal crisis. Renal disease is more likely to occur in the first 5 years of the disease. Scleroderma renal crisis is characterized by malignant hypertension, rapid deterioration of renal function and proteinuria (usually nonnephrotic). Rapid deterioration of renal function alone in the absence of

hypertension can occur in some patients with scleroderma renal crisis. The primary pathogenic process appears to be a renal vasculopathy involving predominantly the interlobular arteries and arterioles (5).

Antiphospholipid syndrome

In addition, a small number of patients with antiphospholipid syndrome can experience kidney problems, which are referred to as extrarenal complications. In APS associated nephropathy, which is the most common extrarenal complication, thrombotic (characterized by blood clots) vascular involvement of the large and intrarenal small-sized vessels of the kidneys occurs. In extreme cases, APS associated nephropathy can progress to acute renal failure. One of the earliest markers of APS associated nephropathy is the inhibition of glomerular filtration. This causes a reduced creatinine clearance and early elevation of the blood urea nitrogen (BUN) and creatinine levels (14).

Sjögren's syndrome

A variety of renal manifestations occur in approximately one-third of patients with primary Sjögren's syndrome, including tubular dysfunction (distal or proximal tubular acidosis, nephrogenic diabetes insipidus), nephrocalcinosis, interstitial nephritis, pseudolymphoma, necrotizing vasculitis and glomerulopathy. Membranous nephropathy and proliferative glomerulonephritis (focal or diffuse, and membranoproliferative) have been reported in primary Sjögren's syndrome. In such cases the possibility of overlap with systemic lupus should be considered (6).

Rheumatoid arthritis

Although early studies described a condition called rheumatoid glomerulonephritis, several investigators have questioned whether a specific nephritis related to rheumatoid arthritis does in fact exist. Mesangial glomerulonephritis has been described in several patients with rheumatoid arthritis who had renal biopsy because of hematuria and/or proteinuria. In a number of patients there is an association between high titers of rheumatoid factor and the occurrence of mesangial nephritis, leading to the hypothesis that the renal lesion represents a functional response of the mesangium to remove IgM rheumatoid factor-IgG complexes. Proliferative glomerulonephritis is extremely rare and may be found in patients with rheumatoid vasculitis (7).

Cryoglobulinemia

Renal complications are common with mixed cryoglobulinemia. Glomerular involvement may develop acutely, particularly after dehydration or

exposure to cold, and may be associated with oliguric acute renal failure. Deposition of cryoglobulins usually occurs in the glomerular subendothelial space. The glomerulonephritis is typically membranoproliferative and/or crescentic in nature (8).

Conclusion

Renal involvement is relatively common in certain systemic autoimmune diseases, but can be clinically silent. Autoimmunity resulting in renal injury

occurs as a systemic disturbance of immunity with the central feature being the loss of tolerance to normal cellular and/or extracellular proteins.

Some of the target autoantigens are now identified in autoimmune diseases where tissue injury includes the kidney. The site of antibody deposition defines the response to injury and clinico-pathological presentation.

The effectors of autoimmunity in the kidney are many, but most often disease is initiated either by antibody deposition or infiltration of immune cells.

References

1. Moore E. Autoimmune diseases and their environmental triggers. Jefferson, NC: McFarland Publishing, 2002.
2. Schlondorff DO. Overview of factors contributing to the pathophysiology of progressive renal disease. *Kidney Int* 2008; 74: 860–6.
3. Segerer S, Kretzler M, Strutz F et al. Mechanisms of tissue injury and repair in renal diseases. In: Schrier R (ed). *Diseases of the kidney and urinary tract*. Lippincott. Philadelphia 2007, Chapter 57.
4. Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from kidney disease, *Kidney Int* 2006; 67: 2089–100.
5. Kettritz R. Autoimmunity in kidney diseases. *Scand J Clin Invest Suppl* 2008; 241: 99–103.
6. O'Callaghan CA. Renal manifestations of systemic autoimmune disease: diagnostic and therapy. *Nephrol Ther* 2006; 3: 140–51.
7. Mason J, Asherson R, Pusey C. The kidney in systemic autoimmune diseases. Elsevier, 2007; p. 432.
8. Mason J, Pusey C. The kidney in systemic autoimmune diseases. In: *Handbook of systemic autoimmune diseases*. Series editor: R. A. Asherson. Elsevier, Oxford 2008; 7: p. 407.
9. Appel GB, Cook HT, Hageman G, et al. Membranoproliferative glomerulonephritis type II (dense deposit disease): an update. *J Am Soc Nephrol* 2005; 16: 1392–403.
10. Sinico RA, Radice A, Corace C, Sabadini E, Bollini B. Anti-glomerular basement membrane antibodies in the diagnosis of Goodpasture syndrome: A comparison of different assays. *Nephrol Dial Transplant* 2006; 21: 397–401.
11. Lou YH. Anti-GBM glomerulonephritis: A T cell-mediated autoimmune disease? *Arch Immunol Ther Exp (Warsz)* 2004; 52: 96–103.
12. Balow JE. Clinical presentation and monitoring of lupus nephritis. *Lupus* 2005; 14: 25–30.
13. Fakhouri F, Noel LH, Zuber J, et al. The expanding spectrum of renal diseases associated with anti-phospholipid syndrome. *American Journal of Kidney Disease* 2003; 41: 1205–11.
14. Vezmar S, Bode U, Jaehde U. Methotrexate-associated biochemical alterations in a patient with chronic neurotoxicity. *Journal of Medical Biochemistry* 2009; 28: 11–15.

Received: January 7, 2010

Accepted: January 30, 2010