02/25

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BANTAO Journal

Official Publication of the BANTAO Association

Incorporating Proceedings of the BANTAO Association

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Published by: Balkan Cities Association of Nephrology, Dialysis, Transplantation and Artificial Organs

Printing: BANTAO, 2025

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BANTAO Journal 2025; 23(2): 21-24

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Editorial

The Bio-Artificial Implantable Kidney

Oana Stirbu[1,2,3], Iancu Viorel Pitea[1] and Mircea Calin Tandrau[1,2,3]

[1]Clinical Emergency County Hospital Arad, Hemodialysis Centre, [2]Vasile Goldis Western University of Arad, [3]Avitum Arad Dialysis Centre, Arad, Romania

Abstract

End-stage kidney disease (ESKD) is a debilitating and costly condition, currently affecting more than 4,5 million people around the globe, with an ascending trend. The currently used treatments for ESKD include single-pass hemodialysis, single-pass peritoneal dialysis, and allograft transplantation. A series of alternative therapies is currently under development, either in preclinical or clinical trials, aiming to increase the performance and affordability of the current treatments or to propose completely new approaches. This article summarizes the latest developments of those alternative therapies, with a focus on the bio-artificial implantable kidney.

Key words: End-stage kidney disease, dialysis, kidney transplantation, alternative therapies, bio-artificial implantable kidney

Introduction

Chronic kidney disease (CKD) has been recently acknowledged as one of the most worrisome threats to global public health due to the increasing number of cases and the associated morbidity and mortality, which are predictably going to steadily increase in the coming years [1-3]. Although tremendous progress has been made toward decreasing the rate of progression to end-stage kidney disease (ESKD) with novel medications aimed at improving kidney survival [4], there are still alarming numbers of people reaching the end of kidney life. This situation requires renal replacement therapies, which currently include single pass hemodialysis, single pass peritoneal dialysis, and allograft transplantation, available globally to no more than a third of the population in need [2,5,6]. This is due to the significant economic burden associated with kidney replacement therapies, especially with dialysis, which is, in fact, the second-best option. Kidney transplantation, which associates much better prognosis and health-related quality of life and hence represents the first option, is facing serious issues related to the shortage of available donor organs and the low eligibility of the ESKD population for receiving a renal graft (no more than 30% of the patients are on the waiting lists) [KDIGO guidelines 2020] [6].

In an effort to increase the availability of therapy and improve the lifespan and quality of life for ESKD patients, new options are the subject of research and have reached preclinical or clinical stages [5,7,8].

Those are: 1) wearable and portable dialysis machines, 2) alternative biological kidneys [xenotransplantation and lab-cultivated human kidney tissue] and 3) a hybrid of the two aforementioned methods, the bio-artificial implantable kidney.

Dialysis improvement and portability

Hemodialysis machines now use at least 120-150 liters of water per dialysis session and also require electricity, making this therapy dependent on water access and purification stations. Peritoneal dialysis uses less water but implies additional patient involvement and required resources and has durability issues. Novel dialysis machines will use sorbent-based techniques [9] for dialysate regeneration and advanced polymeric and inorganic membranes for toxin removal [10] in order to drastically reduce the amount of water required, avoid stationary infrastructure, as well as to improve performance [5,11,12]. This would allow treatments to be performed at home or even provide portability for the dialysis machines. They are currently under clinical trials [3,5].

Alternative biological kidneys:

Xenotransplantation: Attempts to use xenotransplantation as treatment for ESKD in humans started decades ago, with primate organs but failed mainly due to immunological rejection [7].

Clinical trials have been in place since 2024 for xenotransplantation with genetically edited pig kidneys. CRISPR-cas9 technology has been used to remove immunogenic xeno-antigens from the cells of embryonic pigs and to introduce human complement and coagulation regulators [5,13,14].

Correspondence to: Oana Stirbu, Hemodialysis Centre, Clinical Emergency County Hospital Arad, Arad, Romania; E-mail: oanastirbu66@yahoo.com

In 2025, two entities (United Therapeutics and eGenesis) were credited by the FDA in the USA with conducting clinical trials in xenotransplantation, with promising results. A news article published in the journal Nature on September 8th, 2025 [15], reports six-month survival in a human recipient after porcine kidney xenotransplantation, marking an important milestone in this field.
However, the actual clinical availability of the organs poses a few serious concerns in terms of durability, ethics, and the risk of xenosis [13,14,16].
Other obstacles that need to be overcome are the physiological differences between human and pig kidneys, leading to the persistence of erythropoietin deficiency, the inability of pig renin to activate the human RAAS, and the urinary loss of uric acid [14-16]. Those concerns will probably delay the implementation of the treatment by several years [13,14].

Regenerative medicine seeks to restore or replace compromised renal function through the in vitro generation of renal tissue, from human induced pluripotent stem cells (iPSC) as the optimal cellular origin [3,5,7,11].
The principle comes into practice by applying stem cell technologies, tissue engineering, 3D bio-printing, and bioengineering approaches to construct human kidney tissue in the lab [7,17,18].
Human iPSC can be stimulated to develop in the direction of nephrogenic (NPC) and ureterogenic progenitor cells (UPC), from which further specialization leads to the over 20 types of kidney cells that compose the nephron and, respectively, the urinary tract [19].

One of the most important achievements is the development of kidney organoids, that are three-dimensional [3D] multicellular structures generated in vitro from human induced pluripotent stem cells [iPSCs] that self-organize to recapitulate nephrogenesis in the human kidney, including nephron-like units, to the stage of embryonic kidney [in mice] [7,8,18].
Microfluidic organ-on-chip platforms have enabled dynamic perfusion and co-culture of the tubular epithelial cells with human endothelial cells, resulting in enhanced vascular network formation within organoids [7,19].
In October 2025, a team of researchers [8] announced obtaining kidney progenitor assemblies (KPA), a more advanced structure in which the nephrons undergo extensive development and fuse to a centrally located collecting system, recapitulating nephrogenesis up to the stage of a newborn mouse kidney [8].
At this point, however, the lab generated kidney tissue is unable to function independently within a host, lacking the structural and functional complexity required [7].
Producing an organ as complex as the kidney requires specific environment and triggers present in the developing embryo, as well as structures derived from multiple stem cell origins [7,20]. Injecting human iPSC derived cells into developing organs of different animal species in the stage of blastocyst [blastocyst complementation] [21], leads to interspecies chimeric organogenesis and is envisioned as a promising approach to address these challenges in organ production [7,19].
Other promising strategies involve recellularization of decellularized kidney scaffolds [17,22], and cell attachment and differentiation that is improved by chemokines and AKI-CKD cytokine cocktails administered through the ureter and renal artery [21].
Despite all these advances, it appears that developing fully transplantable, functional kidneys remains a formidable and somewhat distant challenge [23]. Critical barriers include precise control over cellular differentiation, tissue organization, and vascularization, as well as translational concerns related to safety, efficacy, ethics and regulatory oversight [19].

The bio-artificial implantable kidney:

The first device using human kidney proximal tubule epithelial cells (PTECs) in an artificial construct was the Renal Assist Device (RAD) [12,24], used in phase I and II clinical studies. For the treatment of a limited number of acute kidney injury patients in an intensive care unit, in the early 2000s [20,24–26], a bioreactor was coupled in series with a conventional hemofilter. The renal cells (PTECs) were layered on the inner surface of the hollow fibers of the bioreactor, in series with a hemofilter and used for continuous renal replacement therapy [24]. Although the experiment was a success, decreasing the mortality of critical patients by more than 30%, the logistical difficulties of manufacturing and maintaining viable cell-based devices, as well as reported thrombocytopenia constituted a redoubtable problem that prevented wider exploring and use of the method [27,28].
The bioartificial implantable kidney (iBAK) is an investigational product under development in both the USA and Europe since 2018. The concept envisions biomimetic membranes that would replicate the glomerular filtration and the presence of live renal epithelial cells to provide tubular functions [29]. As in the real-life kidney, the blood is first filtrated through a semipermeable membrane similar to the one in the glomeruli (the hemofilter component of the iBAK), then the ultrafiltrate will be processed by the PTECs in the bioreactor component. What results is directed to the urinary bladder to be evacuated [27,30]. The iBAK is implanted in the abdominal cavity, in the iliac fossa, connected to the iliac vessels, and it produces urine that is eliminated in the urinary bladder [27]. The purpose of the iBAK is to be used as a long-term substitute for a kidney, in patients with ESKD.
The project requires the application of several advanced technologies: nanotechnology, membrane techno-

logy, stem cell technology, bioengineering, and information technology.
The hemofilter component is created from ultrathin flat sheets of silicone nanopore membranes (SNM) with slit-shaped pores [5-8 nm×2 μm] [10,27,31]. These membranes are assembled in parallel-plate configurations within a hemofilter cartridge, dimensions 11,5/5,7 cm [27], which is then connected to the vascular system for direct blood flow and ultrafiltrate collection. The filtration takes place without the need for a pump other than the heart. The result is an ultrafiltrate that is then processed within the bioreactor [27].
The bioreactor component contains a confluent monolayer of human proximal tubule epithelial cells (PTECs), supported by a synthetic, highly selective silicon nanopore membrane. The bioreactor is engineered for scalability and long-term viability [27,32].
The proof of concept for the bioreactor has been reported by Kim *et al*., in 2023, after successfully implanting bioreactors in pigs and obtaining 90% cell viability at 7 days without the use of anticoagulation or immunosuppression.
The silicon nanopore membrane, which is found in the structure of both components, has unique characteristics [5,10,27,31]. The precisely controlled pore size (5-10 nm) and geometry (slit-shaped or straight channel), allow the membrane to mimic the glomerular filtration barrier and enable selective permeability for water and small solutes while retaining larger proteins, such as albumin [27]. The SNM allows for effective filtration with low driving pressures, such as blood pressure, suitable for implantable applications [10,27]. The structure of the SNM is ultrathin, <1 μm, which minimizes resistance to solute and water transport and supports a compact device design. The surface of the SNM is modified for hemocompatibility with a polyethylene glycol [PEG] fine layer, which is applied by liquid deposition and doesn't obstruct the pores in order to reduce protein fouling and thrombogenicity, potentially reducing or even eliminating the need for anticoagulant therapy [10,27]. The membrane also expresses immunoisolation capacity due to the small size of the pores, providing immunoprotection for the encapsulated renal cells placed on the other side of the SNM [27]. The mechanical robustness of the membrane is achievable despite its thin structure and is needed to withstand physiological blood flow rates and pressures encountered in implantable devices [33].

Basic functions of the ibak

The iBAK performs in a similar manner to the native kidney in terms of the removal of uremic toxins and excess water through mechanical filtration, similar to glomerular function. It is designed to replicate the active reabsorption and secretion of electrolytes and solutes (e.g., sodium, glucose, bicarbonate) by the tubular cells located in the bioreactor. However, the number of inserted tubular cells is smaller than that in the normal kidney due to the spatial limitations of the device and the implantability requirements [10,27].
The tubular cells in the structure of the iBAK are capable to perform metabolic activities, such as the hydroxylation of vitamin D to 1,25-dihydroxyvitamin D and ammonia production [20], but they do not have the ability to produce erythropoietin [27].
The iBAK has multiple advantages compared to conventional renal replacement therapies, as it provides restoration of multiple kidney functions [20,27]. In addition, it confers continuity and autonomy in therapy, similar to a transplanted kidney. The clearance of protein-bound uremic toxins and middle molecules is augmented compared to dialysis [34]. The design of the iBAK reduces the need for immunosuppression and anticoagulation [27]. All things considered, the iBAK has the potential to offer a better quality of life and reduced healthcare costs.
In a recent press release (from 4th November 2025), a representative of the Kidney Project in the USA declared that the initial objective of the project will be to restore kidney function to the level of stage 3 or 4 of CKD and, further, to improve to the final goal of a fully functional kidney.

The realistic outlook for novel kidney replacement therapies development:

Expert consensus suggests that while a "revolution" in kidney replacement therapies is likely before 2040 [35], most advances in the next decade will focus on enhanced dialysis and increased dialysis device portability rather than fully functional bioartificial or regenerated kidneys [5,36]. However, the breakthrough achievements in multiple domains of medical science in recent times allow for hope that radical change is possible for the well-being of ESKD patients.

Conflict of interest statement. None declared.

References:

1. Mark PB, Stafford LK, Grams ME, *et al*. Global, regional, and national burden of chronic kidney disease in adults, 1990–2023, and its attributable risk factors: a systematic analysis for the Global Burden of Disease Study 2023. *The Lancet* 2025; 406(10518): 2461-2482.
2. Romagnani P, Agarwal R, Chan JCN, *et al*. Chronic kidney disease. *Nat Rev Dis Primers* 2025; 11(10: 8.
3. Groth T, Stegmayr BG, Ash SR, *et al*. Wearable and implantable artificial kidney devices for end-stage kidney disease treatment: Current status and review. *Artificial Organs* 2023; 47(4): 649-666.
4. Ng MSY, Hawley CM. A golden year of innovative kidney disease therapeutics. *Nat Rev Nephrol* 2025; 21(2): 75-76.
5. Wieringa FP, Suran S, Søndergaard H, *et al*. The Future of Technology-Based Kidney Replacement Therapies: An

Update on Portable, Wearable, and Implantable Artificial Kidneys. *American Journal of Kidney Diseases* 2025; 85(6): 787-796.
6. Harding JL, Dixon MA, Di M, *et al*. Setting reasonable goals for kidney transplant referral among dialysis facilities. *BMC Nephrol* 2024; 25(1): 235.
7. Huang B, Zeng Z, Zhang CC, *et al*. Approaches to kidney replacement therapies-opportunities and challenges. *Front Cell Dev Biol* 2022; 10: 953408.
8. Huang B, Medina P, He J, *et al*. Spatially patterned kidney assembloids recapitulate progenitor self-assembly and enable high-fidelity in vivo disease modeling. *Cell Stem Cell* 2025; 32(10): 1614-1633.e13.
9. Fabiani T, Zarghamidehaghani M, Boi C, *et al*. Sorbent-based dialysate regeneration for the wearable artificial kidney: Advancing material innovation via experimental and computational studies. *Separation and Purification Technology* 2025; 360: 130776.
10. Kensinger C, Karp S, Kant R, *et al*. First Implantation of Silicon Nanopore Membrane Hemofilters. *ASAIO Journal* 2016; 62(4): 491-495.
11. Ramada DL, De Vries J, Vollenbroek J, *et al*. Portable, wearable and implantable artificial kidney systems: needs, opportunities and challenges. *Nat Rev Nephrol* 2023; 19(8): 481-490.
12. Fissell WH, Roy S, Davenport A. Achieving more frequent and longer dialysis for the majority: wearable dialysis and implantable artificial kidney devices. *Kidney International* 2013; 84(20): 256-264.
13. (*Editorial – no authors listed*) A tipping point for kidney xenotransplantation. *Nat Med* 2025; 31(7): 2075.
14. Kaiser M, Gunther P, Forsberg EM, *et al*. Is Europe ready for xenotransplantation? *Humanit Soc Sci Commun* 2024; 11(1): 1582.
15. Fieldhouse R. 'Amazing feat': US man still alive six months after pig kidney transplant. *Nature* 2025; 645(8081): 571-572.
16. Lee SA, Lafargue MC, Williams WW, *et al*. Physiologic Homeostasis in a Living Human after Pig Kidney Xenotransplantation. *Nat Commun* 2025; 16(1): 8453.
17. Xu W, Yi F, Liao H, *et al*. The Potential and Challenges of Human Pluripotent Stem Cells in the Treatment of Diabetic Nephropathy. *Front Biosci [Landmark Ed]* 2025; 30(4): 28283.
18. Chia HN, Wu BM. Recent advances in 3D printing of biomaterials. *J Biol Eng* 2015; 9: 4.
19. Vigezzi A, Brani P, Dalla Gasperina D, *et al*. Preclinical approaches in regenerative medicine for treating end-stage renal disease: a scoping review. *Front Endocrinol* 2025; 16: 1549744.
20. Humes HD, Buffington D, Westover AJ, *et al*. The bioartificial kidney: current status and future promise. *Pediatr Nephrol* 2014; 29(3): 343-351.
21. Choi M, Al Fahad MA, Shanto PC, *et al*. Surface modification of decellularized kidney scaffold with chemokine and AKI-CKD cytokine juice to increase the recellularization efficiency of bio-engineered kidney. *Biomaterials* 2025; 316: 123007.
22. Salti H, Nelz SC, Lichtwark S, *et al*. Recellularization of scaffolds derived from precision-cut kidney slices. *Biomed Mater* 2025; 20(6): 1-16.
23. Xi Y, Song W. Kidney organoids in translational research: disease modeling, drug discovery, and unresolved challenges. *Cell Tissue Res* 2025; 402: 303-312.
24. Tumlin J, Wali R, Williams W, *et al*. Efficacy and safety of renal tubule cell therapy for acute renal failure. *J Am Soc Nephrol* 2008; 19(5): 1034-1040.
25. Song JH, Humes HD. The bioartificial kidney in the treatment of acute kidney injury. *Curr Drug Targets* 2009; 10(12): 1227-1234.
26. Jansen J, Fedecostante M, Wilmer MJ, *et al*. Biotechnological challenges of bioartificial kidney engineering. *Biotechnol Adv* 2014; 32(7): 1317-1327.
27. Kim EJ, Chen C, Gologorsky R, *et al*. Feasibility of an implantable bioreactor for renal cell therapy using silicon nanopore membranes. *Nat Commun* 2023; 14(1): 4890.
28. Fissell WH, Roy S. The implantable artificial kidney. *Semin Dial* 2009; 22(6): 665-670.
29. Roy S, Goldman K, Marchant R, *et al*. Implanted renal replacement for end-stage renal disease. *Panminerva Med* 2011; 53(3): 155-166.
30. Humes HD, MacKay SM, Funke AJ, Buffington DA. Tissue engineering of a bioartificial renal tubule assist device: in vitro transport and metabolic characteristics. *Kidney Int* 1999; 55(6): 2502-2514.
31. Fissell WH, Dubnisheva A, Eldridge AN, *et al*. High-Performance Silicon Nanopore Hemofiltration Membranes. *J Memb Sci* 2009; 326(1): 58-63.
32. Cheng Y, Luo Q, Hong J, *et al*. Size-controlled fabrication of silicon nanopore arrays by silver-assisted chemical etching. *J Chem Phys* 2025; 162(17): 174702.
33. Nasa S, Varma M. Buried Nanopore Membranes with Enhanced Mechanical Robustness for High-Resolution Single-Molecule Sensing. *Nano Lett* 2025; 25(49): 17016-17024.
34. Faria J, Ahmed S, Stamatialis D, *et al*. Bioengineered Kidney Tubules Efficiently Clear Uremic Toxins in Experimental Dialysis Conditions. *Int J Mol Sci* 2023; 24(15): 12435.
35. Pereira Cabral B, Bonventre JV, Wieringa F, Mota FB. Probing expert opinions on the future of kidney replacement therapies. *Artif Organs* 2021; 45[1]: 79-87.
36. Bonventre JV, Hurst FP, West M, *et al*. A Technology Roadmap for Innovative Approaches to Kidney Replacement Therapies: A Catalyst for Change. *Clin J Am Soc Nephrol* 2019; 14(10): 1539-1547.

BANTAO Journal 2025; 23(2): 25-27

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Review

Collateral Renal Injury: Is Nephrotoxicity the Inevitable Cost of Anti-VEGF and ICI Synergy?

Vasiliki Gkika[1,2] and Goce Spasovski[3]

[1]Private Nephrology Practice, Panormou, Athens, Greece, [2]Frontis Dialysis Center, Piraeus, Greece, [3]University Department of Nephrology, Medical Faculty, University Sts Cyril and Methodius, Skopje, N Macedonia

Abstract

Antiangiogenic therapies and immune checkpoint inhibitors (ICIs) have improved cancer outcomes but may cause kidney adverse events.

This mini-review summarizes the mechanisms, clinical manifestations, and management of nephrotoxicity associated with anti-vascular endothelial growth factor (VEGF) agents, VEGFR-targeted multikinase inhibitors, and ICIs.

The mechanisms of kidney injury differed according to the therapeutic class. VEGF pathway inhibition disrupts glomerular barrier integrity, leading mainly to hypertension, proteinuria, kidney dysfunction, and thrombotic microangiopathy. Multikinase inhibitors may also cause electrolyte abnormalities. ICIs most commonly induce acute interstitial nephritis, although glomerular diseases, including pauci-immune glomerulonephritis, podocytopathies, and C3 glomerulonephritis, have also been reported. Combined anti-VEGF and ICI treatment may further increase the risk of proteinuria. Management depends on the type and severity of kidney injury and may require treatment interruption, kidney biopsy, glucocorticoids, or other immunosuppressive therapies.

Early recognition and multidisciplinary management may mitigate nephrotoxicity while preserving optimal oncological treatment.

Keywords: angiogenesis inhibitors, anti-VEGF therapies, Immune checkpoint inhibitors, acute kidney injury

Introduction

Significant progress in the field of cancer therapy has been made in the last several years by using angiogenesis inhibitors, anti-VEGF therapies, both as monotherapy and in combination with other anticancer therapies such as Immune checkpoint inhibitors (ICIs). Although these agents have revolutionized the treatment of cancer and are now the backbone of therapy for several malignancies, their use is associated with possible kidney consequences such as proteinuria and acute kidney injury (AKI). Given that patients with preexisting cardiovascular disease and kidney impairment are often excluded from clinical trials of cancer therapies and that the patients who are enrolled in trials are usually in better overall health condition, the incidence of adverse events is likely to be underestimated in clinical practice.

In this mini review, we discuss the relationship between kidney function and specific antineoplastic agents, with a focus on their toxic effects.

Molecularly targeted therapies

Vascular Endothelial Growth Factor (VEGF) is the key driver of tumour-related angiogenesis and acts through interaction with VEGF receptors (VEGFRs) expressed on tumour endothelial cells. Importantly, VEGF is also expressed on glomerular podocytes, distal tubules, and collecting ducts. The VEGF pathway plays a role in the substantial cross talk that exists between podocytes and endothelial cells that enables appro/priate glomerular filtration and perfusion. Podocytes release VEGF, which can then bind VEGFR-2 on the glomerular endothelial cells. VEGF is involved in the proliferation, differentiation, and survival of mesangial and endothelial cells, and has a pivotal role in maintaining the structure and function of the glomerular barrier. In its absence, podocytes and endothelial cells are unable to mature and proliferate, which prevents the formation of capillaries and veins. The reduced production of VEGF by podocytes induces the loss of glomerular and mesangial cells [1-3]. Notably, the pleiotropic effect of VEGF on kidneys accounts for all the different histological effects of anti-VEGF agents (endotheliosis, glomerulosclerosis, hyalinosis, different types of glomerulonephritis, and thrombotic microangiopathies [2]).

Correspondence to: Vasiliki Gkika, Private Nephrology Practice, Panormou, Athens, Greece; E-mail: vasilikigkika91@gmail.com

Common kidney side effects of **anti-VEGF drugs** include proteinuria, hypertension, kidney dysfunction, thrombotic microangiopathy, and in some cases, kidney failure [2,3]. The development of proteinuria induced by anti-VEGF agents is thought to be driven by a combination of glomerular endothelial cell damage, podocyte dysfunction, and hemodynamic alterations.
More specifically, loss of the normal control of VEGF-A expression, leads to structural and functional changes in glomerular cells. In addition, antagonism of VEGF dysregulates kidney–repair processes in the early stages of renal damage, thus increasing the risk of glomerulosclerosis. In addition, the inhibition of VEGF leads eventually to a loss of selective glomerular permeability. Proteinuria might also be caused by increased intraglomerular pressure secondary to arterial hypertension [1]. The binding of VEGF to its receptors increases vascular permeability, induces cell division and differentiation, and blocks apoptosis and cellular ageing. Consequently, VEGF inhibition reduces the ability of cell renewal, increases apoptosis in vascular endothelial cells, promotes rarefaction of capillaries and arterioles, and interferes with the cellular production of vasodilators, such as nitric oxide and prostacyclin, favoring vasoconstriction, increased peripheral resistance and decreased renal excretion of sodium [1]. The main driver of VEGF inhibitor induced hypertension and kidney toxicities seems to be an upregulation in endothelin (ET)-1 via the stimulation of the ETA receptor. This in turn, contributes to the increases in reactive oxygen species (ROS) and a reduction in nitric oxide (NO). Paradoxically, treatment with an anti-VEGF agent leads to an increase in prostacyclin (PGI2), which may be driven by an upregulation in both cyclooxygenase (COX)-1 and COX-2. ET-1 may also contribute to the increase in PGI2. The upregulation in PGI2 and stimulation of its receptor, the prostanoid (IP) receptor, may act as a compensatory effect to counteract the kidney effects of ET-1/ETA receptor stimulation. However, very high levels of PGI2 may then cause deleterious effects via stimulation of other prostanoid receptors such as the thromboxane (TP) or e-prostanoid $(EP)_{2\text{-}4}$ receptors [3].
Furthermore, there are **multikinase inhibitors** that target VEGFRs and other receptors involved in tumour vascularization. Multiple mechanisms could be involved in the pathogenesis of hypertension associated with these agents, such as abnormalities of the nitric oxide pathway, endothelial dysfunction and capillary rarefaction. Endothelial dysfunction accounts also for the development of proteinuria [1]. Moreover, these inhibitors have been associated with an increased incidence of electrolyte abnormalities, such as hypophosphataemia, hypocalcaemia and hyponatraemia.

Immune checkpoint inhibitors (ICIs)

Immune checkpoint inhibitors (ICIs) are primarily humanized or human IgG1 k or IgG4 k [4]. Kidney and liver dysfunction do not affect ICI clearance, they are not dialyzable and their half-life ranges from 7 to 27 days [5]. ICIs disrupt the normal immune regulatory checkpoints, leading to an activation of T cells against tumor cells. This can target kidney tissue, leading to an enhanced immune response and causing kidney injury. In addition, the production of autoantibodies and the formation of immune complexes can further exacerbate renal damage.
Immune checkpoint inhibitors (ICIs) are associated with a spectrum of renal immune-related adverse events (irAEs) including acute kidney injury (AKI), most commonly manifesting as acute interstitial nephritis (AIN), although glomerular disease and electrolyte disturbances have also been reported [6].
The most common types of glomerular lesions that have also been described that were pauci-immune glomerulonephritis/renal vasculitis (27%), podocytopathies, including minimal change disease and focal segmental glomerular sclerosis (24%), and C3 glomerulonephritis (11%) [7].
Although ICI use in patients with advanced chronic kidney disease (CKD) and end-stage kidney disease is no contraindicated, close monitoring is warranted, especially in patients with CKD, as the development of AKI may lead CKD progression and increased mortality [8].

Combination Therapy: anti-VEGF Agent and Immune Checkpoint Inhibitor

In recent years, anti-VEGF agent and ICI combination therapies have emerged rapidly in the oncologic field. The rationale for this combination lies in the **synergistic** effects of the two treatment modalities. Together, these treatments make the immune system more effective at attacking cancer cells [3]. There was a statistically significant higher rate of grade ≥ 3 proteinuria associated with the ICI-TKI combinations when compared to VEGF-TKI alone [9].

Management

While discontinuation of the **anti-VEGF Agent** (Table 1) results in significant reduction in proteinuria, persistence is common. Lowering of intraglomerular pressure may reduce protein excretion. There are no randomized controlled trials evaluating the benefit of agents, such as renin-angiotensin aldosterone system blockade in patients with proteinuria due to antiangiogenic agents [10]. Given the evidence that activation of the ET system is integral to the development of

hypertension and kidney damage during anti-VEGF therapy, it seems that targeting the downstream effects of activation of the ET pathway may be a viable therapeutic option [3].

Table 1. Classification of anti-VEGF agents and immune checkpoint inhibitors

Drug class	Mechanism	Agents
Anti-VEGF agents	VEGF pathway inhibitors	Bevacizumab, Ramucirumab, Aflibercept
Multi-kinase inhibitors (VEGFR-targeted TKIs)	VEGFR tyrosine kinase inhibitors	Sunitinib, Sorafenib, Pazopanib, Axitinib, Cabozantinib, Lenvatinib, Regorafenib, Vandetanib, Tivozanib, Fruquintinib, Ponatinib
Immune checkpoint inhibitors (ICIs)	Anti-PD-1	Cemiplimab, Dostarlimab, Nivolumab, Pembrolizumab, Penpulimab, Retifanlimab, Tislelizumab, Toripalimab
	Anti-PD-L1	Atezolizumab, Avelumab, Cosibelimab, Durvalumab
	Anti-CTLA-4	Ipilimumab, Tremelimumab
	Anti-LAG-3	Relatlimab, nivolumab

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitor; LAG-3, lymphocyte-activation gene 3; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

The treatment of **ICI-AKI** (Table 1) depends on the severity and histopathologic subtype of injury (AIN, glomerular pathology). All patients require immediate cessation of drugs that are known to cause AIN (e.g., nonsteroidal anti-inflammatory drugs, PPIs, or antibiotics). For patients with stage 2 AKI or higher severity and strong clinical suspicion of ICI-AKI, immediate cessation of ICI therapy is advised, followed promptly by a plan for a kidney biopsy and the initiation of glucocorticoids. Alternate immunosuppressants such as infliximab [8] should be also used. In patients with ICI-glomerulonephritis it is suggested that nonsteroidal immunosuppressive therapy, such as rituximab, in combination with glucocorticoids [11] are to be used. Consequently, an appropriate prophylaxis for pneumocystis jirovecii pneumonia is advised for patients receiving immunosuppressive therapy. The pivotal decision to ICI **rechallenge** needs to be individualized, considering various factors, such as severity of initial ICI-AKI, other extrarenal irAEs, and the availability of alternative treatment options [8].

Conflict of interest statement. None declared.

References

1. Porta C, Cosmai L, Gallieni M, *et al*. Renal effects of targeted anticancer therapies. *Nature Reviews Nephrology* 2015; 11(6): 354-370.
2. Tian J, Lian X, Wang Y. Anticancer drug-induced nephrotoxicity: Biopsy-proven patterns and outcomes across chemotherapy, targeted therapy, and immune checkpoint inhibitors. *Renal Failure* 2025; 47(1): 2590283.
3. Zhang L, Chen M. Mechanisms of anti-VEGF therapy-induced kidney injury: Current insights and future perspectives in combination with immune checkpoint inhibitors. *American Journal of Physiology-Renal Physiology* 2025; 329(2): F112-F125.
4. Wang X, Liu Y. A review of the pharmacokinetic characteristics of immune checkpoint inhibitors and their clinical impact factors. *Pharmacogenomics and Personalized Medicine* 2023; 16, 55-68.
5. Picardo F, Taraszka K, Weinberg BA. Structure and optimization of checkpoint inhibitors. *Cancers* 2019; 12(1): 38.
6. Gupta S, Garcia-Carro C, Mitchell AP, *et al*. Acute kidney injury in patients treated with immune checkpoint inhibitors. *Journal for ImmunoTherapy of Cancer* 2021; 9(10): e003467.
7. Kitchlu A, Fingrut W, Avila-Casado C, *et al*. A systematic review of immune checkpoint inhibitor–associated glomerular disease. *Kidney International Reports* 2021; 6(1): 66-77.
8. Gupta S, American Society of Onconephrology. Diagnosis and management of immune checkpoint inhibitor-associated nephrotoxicity: A position statement from the American Society of Onconephrology. *Kidney International* 2025; 107(1): 21-32.
9. Dukkipati A, Li X, Gupta S. Nephrotoxicity associated with contemporary renal cell carcinoma regimens: A systematic review and meta-analysis. *Kidney Cancer* 2023; 7(1): 1-15.
10. Gupta S, Schmidt A, Glezerman IG, *et al*. Risk factors for severe hypertension and proteinuria after treatment with vascular endothelial growth factor signaling pathway inhibitors among patients with cancer. *Kidney International Reports* 2024; 9(6): 1640-1651.
11. Mamlouk O, Lin JS, Abdelrahim M, *et al*. Checkpoint inhibitor-related renal vasculitis and use of rituximab. *Journal for ImmunoTherapy of Cancer* 2020; 8(2): e000750.

BANTAO Journal 2025; 23(2): 28-30

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Original article

The Role of SGLT2 Inhibitors In the Complex Treatment of Patients with CKD – The Results of one Tertiary Center

Yordan Vlahov[1], Ivana Kalinkova[2], Victoria Kotseva[2], Neli Koleva[2], Atanas Kundurdjiev[2] and Milena Nikolova[2]

[1]Clinic of Endocrinology and Metabolism, Sofiamed University Hospital, [2]Clinic of Nephrology, St. Iv. Rilski University Hospital, Sofia, Bulgaria

Abstract

Introduction. Chronic kidney disease (CKD) represents a major and increasing social and economic problem, as it affects between 6 and 18% of the population worldwide and is associated with a high cardiovascular risk, morbidity and mortality. SGLT2-inhibitors have central role in the complex treatment of patients with CKD of different etiology, as first-line nephroprotective agents both in patients with and without concomitant or underlying diabetes mellitus. The aim of our study was to evaluate the effects of two commercially available SGLT2-inhibitors (dapagliflozine and empagliflozine) on renal parameters in patients with CKD and biopsy-proven glomerular diseases at the background of standard treatment in a real-life observational study.

Methods. In 2024 we observed 54 CKD patients (33 males, aged 19-85 years) treated with SGLT2-inhibitors (dapagliflozine and empagliflozine registered for standard-of-care treatment of CKD in our country) for 6 months, at the background of standard treatment for the underlying disease. All patients had CKD, with biopsy-proven renal disease: 20 had diabetic nephropathy at the background of type 2 diabetes mellitus (DM2), 4 had systemic amyloidosis with renal involvement (2 had AA and 1 had AL type), 20 had biopsy-proven glomerulonephritis, and 10 had hypertensive nephropathy. Three of the patients with glomerulonephritis had concomitant DM2. Overall, 38 received dapagliflozine and 16 were on empagliflozine. All patients were followed for 3 months and 32/54 were followed until month 6. The patients were evaluated at the initiation of the treatment and at 3 and 6 months. All patients received standard-of-care treatment for the renal and accompanying diseases. Written informed consent was obtained from all patients prior to any medical procedures.

Results. During the follow-up we observed stabilization of renal function with no significant changes in serum creatinine and eGFR, a decrease in serum uric acid levels and proteinuria, with no significant side effects. These effects showed no differences between male and female patients and across the different disease entities.

Conclusion. The results of our study are confirmatory in nture and support the use of SGLT2-inhibitors as nephroprotective agents and across various CKD entities.

Keywords: chronic kidney disease, SGLT2-inhibitors, nephroprotection, diabetes, glomerulonephritis, hypertensive nephropathy, uric acid, proteinuria

Introduction

Chronic kidney disease (CKD) is defined as presence of kidney damage (based on laboratory, imaging or histopathological data) or an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² or markers of kidney damage (albuminuria, pathological urinary sediment, abnormal imaging results, tubular disorders, or a history of kidney transplantation), persisting for at least 3 months, irrespective of the cause [1]. CKD represents a major and increasing social and economic problem, as it affects between 6 and 18% of the population worldwide and is associated with high cardiovascular risk, morbidity and mortality [2]. SGLT2-inhibitors have central role in the complex treatment of patients with CKD of different etiology, as first-line nephroprotective agents both in patients with and without concomitant or underlying diabetes mellitus [3,4]. The aim of our study was to evaluate the effects of SGLT2-inhibitors on renal parameters in patients with CKD and biopsy-proven glomerular diseases at the background of standard treatment in a real-life observational study, first one at our institution.

Materials and methods

In 2024 we observed 54 CKD patients treated with two available SGLT2-inhibitors (dapagliflozine and empa-

Correspondence to: Milena Nikolova, Clinic of Nephrology, St. Iv. Rilski University Hospital, Sofia, Bulgaria, E-mail: milena_i_dani@abv.bg

gliflozine registered for standard-of-care treatment of CKD in our country), at the background of standard treatment for the underlying disease, for a period of 6 months. Our group consisted of 54 patients (33 males, aged 19-85 years). All patients had CKD [1,2], with biopsy-proven renal disease: 20 had diabetic nephropathy at the background of type 2 diabetes mellitus (DM2), 4 had systemic amyloidosis with renal involvement (2 had AA and 1 had AL type), 20 had biopsy-proven glomerulonephritis (GN) [6-IgA GN, 5-focal and segmental glomerulosclerosis (FSGS), 5-systemic lupus erythematosus (SLE) with lupus nephritis (LN), 2-mesangioproliferative GN, 1-primary membranous GN (MGN), 1-polyangiitis with granulomatosis, and 10 had hypertensive nephropathy]. Three of the patients with glomerulonephritis had concomitant DM2. Overall, 38 received dapagliflozine and 16 were on empagliflozine. All patients were followed for 3 months and 32/54 were followed until month 6. The patients were evaluated at the initiation of the treatment and at 3 and 6 months. All patients received ACE-inhibitor or AT2-blocker, all patients with GN received pathogenetic treatment, according to the standard treatment protocols, amyloidosis patients received also colchicine treatment. None of the diabetic patients was on insulin treatment, and they received standard-of-care treatment for DM2, in accordance with the accepted Good Clinical Practice guidelines in Bulgaria [5]. Following parameters were evaluated, using standard methods: hemogram (complete blood count), biochemical investigations of the blood (creatinine, urea, uric acid, lipidogram, fasting blood glucose, potassium, sodium, chlorides, calcium, phosphates, liver enzymes (ASAT, ALAT, GGT, Alkaline phosphatase), total protein and serum albumin levels), urine investigations (proteinuria, urinalysis, if needed-microbiological investigation of the urine), estimated glomerular filtration rate (eGFR, according to the MDRD formula [6]). The statistical analysis was performed using a standard SPSS 27 pack for Windows. Written informed consent was obtained from all patients prior to any medical procedures.

Results

There was stabilization of serum creatinine and eGFR (Figure 1), decrease in proteinuria (Figure 2), and reduction in uric acid levels (Figure 3) in the majority of patients (Table 1). A sole statistically significant diffe-

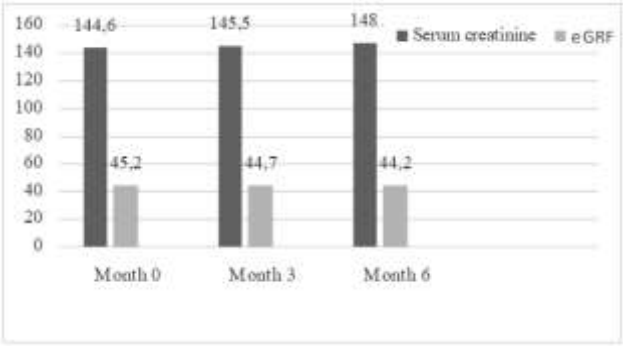


Figure 1. Changes in the mean serum creatinine (μmol/L) and eGFR (ml/min/1.73 m^2, calculated according using the MDRD formula) during the 6 months treatment. p=NS for all comparisons

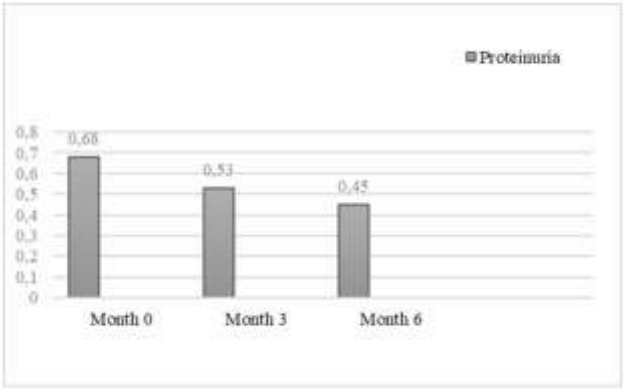


Fig. 2. Changes in the mean levels of proteinuria (g/L) during the 6 months treatment. p=NS for all comparisons

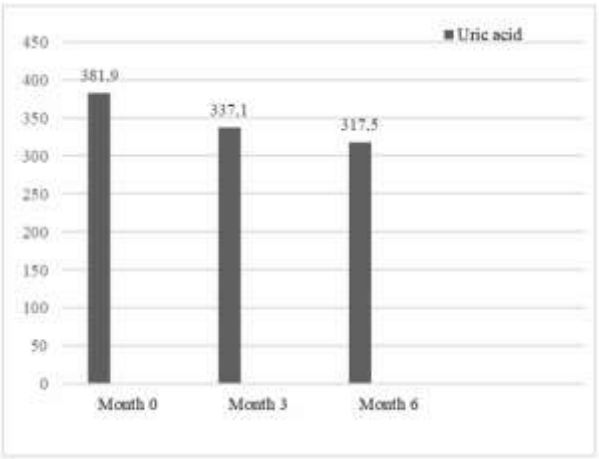


Fig. 3. Changes in the mean serum uric acid levels (μmol/L) during the 6 months of treatment. For comparisons at month 0 vs month 3 and 6 - $p<0.05$; for comparison at month 3 vs month 6 p=NS (>0.05)

Table 1. Changes in mean levels of serum creatinine (mcmol/l), GFR (ml/min/1.73 m^2, calculated using the MDRD formula), uric acid (μmol/L) and proteinuria (g/L) during the 6-months treatment (**p<0.05 for changes in uric acid levels** – month 0 vs month 3 and 6; p=NS for the rest).

Months	Serum creatinine (μmol/L)	eGFR (ml/min/1.73 m^2)	Serum uric acid (μmol/L)	Proteinuria (g/L)
0 (54 patients)	144.6 +/- 56.7	45.2 +/- 20	381.9 +/- 121.3	0.68 +/- 1.5
3 (54 patients)	145.5 +/- 58.8	44.7 +/- 20.4	337.1 +/- 82	0.53 +/- 1.2
6 (32 patients)	148 +/- 59.6	44.2 +/- 20.4	317.5 +/- 79.2	0.45 +/- 1.1

rence was observed between the levels of the uric acid at months 0 and 3, and months 0 and 6 (figure 3), without a statistically significant difference between months 3 and 6 (figure 3). There were no changes in hemogram, serum electrolytes, calcium and phosphate levels, total protein and serum albumin levels, blood glucose and liver enzymes levels during the follow-up. Only 3 patients developed lower-urinary-tract infections that did not lead to discontinuation of the treatment. We observed no cases of hypoglycemia, ketoacidosis or significant worsening of renal function. There was no treatment discontinuation in any of the patients.
We found no difference in the effect of both SGLT2-inhibitors in men and women and across different disease entities.

Discussion

SGLT2-inhibitors are one of the widely accepted nephroprotective strategies both in patients with diabetic and non-diabetic CKD [3]. They have beneficial effect on renal function, proteinuria and uric acid levels mediated via their hypoglycemic, hemodynamic and pleiotropic effects, including effects on glomerular structures and endothelial cells [3,4].
The results of our observational study confirm the beneficial effects of two SGLT2-inhibitors in patients with CKD of different etiology (both diabetic and non-diabetic) with statistically significant decrease of uric acid levels. The reduction in proteinuria did not reach significant level and the creatinine and GFR were stabilized. There were no side effects detected.
Our study included a small number of CKD patients that were followed up for only 6 months. Therefore, two major limitations in our study were the small cohort and short observational period. Nevertheless, our results revealed a stabilization of renal function, i.e. a decrease in the rate of renal function loss, with a decrease of both hyperuricemia and urine protein loss. Further studies in larger cohorts and longer observation periods are needed for the validation of these results.

Conclusion

In conclusion, the results of our small study in patients with CKD with different etiology and biopsy-proven glomerular involvement, revealed the beneficial effects of the two commercially available SGLT2-inhibitors used for nephroprotection-stabilization of renal functional parameters and decrease in serum uric acid levels and proteinuria, two well-known risk factors for progression of both CKD and cardio-vascular complications. The absence of significant side effects of treatment and our results are in favor of the use of these medications in patients with CKD of different origin.
This was an investigator-driven study and has no commercial support. The authors have no conflicts of interest, associated with this study. The results of the current study were presented as electronic poster at the CaReMeLO 2025 Conference, Warsaw, Poland, 30-31 May, 2025.

Conflict of interest statement. None declared.

References

1. Vaidya SR, Aeddula NR. Chronic Kidney Disease. *In: StatPearls* https://www.ncbi.nlm.nih.gov/books/NBK535404/.
2. Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management: A Review. *JAMA* 2019; 322(13): 1294-1304.
3. Gajewska A, Wasiak J, Sapeda N, *et al*. SGLT2 Inhibitors in Kidney Diseases-A Narrative Review. *Int J Mol Sci* 2024; 25(9): 4959.
4. Granata A, Pesce F, Iacoviello M, *et al*. SGLT2 Inhibitors: A Broad Impact Therapeutic Option for the Nephrologist. *Front Nephrol* 2022; 2: 867075.
5. Recommendations for good clinical practice for the treatment of diabetes mellitus. Bulgarian society of endocrinology, 2019, Accessible at: https://endo-bg.com/wp-content/uploads/2019/10/endo-zaharen-diabet-2019.pdf.
6. Levey AS. A More Accurate Method To Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation. *Ann Intern Med* 1999; 130: 461-470.

BANTAO Journal 2025; 23(2): 31-35

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Original article

Post-COVID Trajectory and Outcomes of Chronic Kidney Disease

Tatiana Razlog[1], Eugeniu Russu[1,2], Larisa Rotaru[2], Emil Ceban[3], Costina Groza[1] and Liliana Groppa[2]

[1]Timofei Moșneaga Republican Clinical Hospital, [2]Department of Rheumatology and Nephrology, Nicolae Testemițanu State University of Medicine and Pharmacy, [3]Department of Urology and Surgical Nephrology, Nicolae Testemițanu State University of Medicine and Pharmacy, Chișinău, Republic of Moldova

Abstract

Introduction. COVID-19 is a multisystem disease with frequent renal involvement. Acute SARS-CoV-2 infection can precipitate acute kidney injury (AKI) and accelerate chronic kidney disease (CKD), while pre-existing CKD worsens COVID-19 outcomes. We evaluated post-COVID CKD trajectory and key risk factors for CKD progression and adverse outcomes in survivors.

Methods. We performed a retrospective observational study of 1,000 adults hospitalized with COVID-19 at *Timofei Moșneaga* Republican Clinical Hospital (2020-2022). Clinical data and inflammatory, renal and hepatic parameters were collected during acute illness. CKD stage was defined by estimated glomerular filtration rate (eGFR) according to KDIGO. "CKD progression" was defined as transition to a more advanced CKD stage or new-onset CKD stage ≥3 during follow-up. Patients with versus without CKD progression was compared, and multivariate models identified independent predictors of CKD progression and mortality.

Results. CKD progression occurred in 30% of patients during a median 12-month follow-up. Progressors were older (median 71 vs 62 years, p<0.001) and more frequently had hypertension (74% vs 62%, p=0.005), type 2 diabetes (27% vs 21%, p=0.017) and cardiovascular disease (31% vs 23%, p=0.04). Comorbidity burden was higher (Charlson index 5 vs 3, p<0.0001). Baseline CKD conferred >2.5-fold higher risks of mortality and further renal decline than absence of CKD.

Conclusions. COVID-19 was associated with accelerated CKD progression in survivors, especially in older, comorbid patients. Advanced age, hypertension, cardiovascular disease, type 2 diabetes and Charlson index >4 independently predicted poor renal and survival outcomes, supporting close nephrological follow-up and nephroprotective strategies in high-risk post-COVID patients.

Keywords: COVID-19; chronic kidney disease; acute kidney injury; CKD progression; risk factors; outcomes

Introduction

COVID-19, initially viewed as a respiratory illness, is now recognized as a multisystem disease with long-term organ sequelae [1]. Renal involvement is significant: acute COVID-19 frequently causes acute kidney injury (AKI), reported in ~30-50% of hospitalized patients [1,2], and AKI markedly increases the risk of chronic kidney disease (CKD) development or progression [2,3]. Patients with pre-existing CKD are particularly vulnerable, with COVID-19 mortality more than double that of individuals without kidney disease [3]. Thus, the relationship between COVID-19 and CKD is bidirectional-acute infection may cause persistent renal damage, while underlying CKD worsens COVID-19 outcomes.

Evidence also shows increased long-term renal impairment among COVID-19 survivors, even in the absence of AKI [4,5]. Large cohort studies indicate higher rates of incident CKD and accelerated eGFR decline after COVID-19 compared with other pneumonias [6], especially in older patients and those with hypertension or diabetes [6,7]. These comorbidities further exacerbate kidney injury through inflammatory, hemodynamic, and metabolic mechanisms [3,7].

The concept of "renal long COVID", encompassing new or progressive CKD following SARS-CoV-2 infection, has gained prominence [4,5], though true incidence remains uncertain due to small cohorts, short follow-up periods, and heterogeneous CKD definitions [4,5]. Data from Eastern Europe are particularly limited, despite the global burden of CKD and its major public health implications [1,3,5].

The present study investigated a large cohort of hospitalized COVID-19 survivors with the following objectives: (1) to determine the frequency of AKI occurring during acute COVID-19 and the progression or worsening of pre-existing CKD after recovery, acknow-

Correspondence to: Tatiana Răzlog, Timofei Moșneaga Republican Clinical Hospital, Str. Nicolae Testemițanu 29, MD-2025 Chișinău, Republic of Moldova; E-mail: nedoreat@gmail.com

ledging that de novo CKD cannot be diagnosed in patients without prior kidney disease within a short post-infectious timeframe; (2) to identify clinical and laboratory predictors associated with AKI development during COVID-19 and subsequent renal function deterioration; and (3) to assess the impact of baseline CKD on COVID-19-related in-hospital mortality. We hypothesized that older patients with multiple comorbidities are at increased risk of AKI during acute infection, accelerated CKD progression after recovery, and poorer clinical outcomes**.**

Material and methods

Study design and population: We conducted a retrospective observational study of 1,000 adults hospitalized with RT-PCR-confirmed COVID-19 at Timofei Moșneaga Republican Clinical Hospital (Chișinău, Moldova) between March 2020 and December 2022. Inclusion criteria were age ≥18 years and availability of post-COVID renal follow-up. Patients on chronic dialysis or kidney transplant recipients were excluded. Pre-existing CKD (stages 1-4) was identified from medical records; CKD was defined as eGFR <60 mL/min/1.73 m^2 or structural kidney disease >3 months per KDIGO.

Data collection: Demographics, comorbidities (hypertension, diabetes, cardiovascular disease, obesity), and Charlson Comorbidity Index were recorded. CVD was defined as coronary artery disease, heart failure, or stroke; obesity as BMI ≥30 kg/m^2. Laboratory data during acute illness included inflammatory markers, renal and hepatic tests. AKI was defined by KDIGO criteria with highest AKI stage was noted. Severity was assessed by ICU admission or mechanical ventilation. After discharge, patients underwent scheduled renal follow-up (creatinine, eGFR, urine tests) at ~3, 6, and 12 months. CKD progression was defined as transition to a more advanced KDIGO stage or new-onset CKD ≥stage 3 in previously healthy patients, and for those with CKD, any stage that increases or ≥25% eGFR decline constituted progression. Mortality and initiation of dialysis were recorded. Median follow-up was ~12 months (IQR 9-15).

Statistical analysis: Patients were stratified into progression vs. non-progression groups. Group comparisons used t-tests or Mann-Whitney U tests for continuous variables and chi-square or Fisher's exact tests for categorical variables (significance $p<0.05$). Multivariate logistic regression identified independent predictors of CKD progression (age, sex, baseline CKD, hypertension, diabetes, obesity, CVD, Charlson index, AKI). Cox models assessed predictors of mortality, including baseline CKD and CKD progression. Proportional hazards assumptions were met. Results are expressed as ORs or HRs with 95% CIs. Analyses were performed using STATISTICA 9.0 and SPSS 26.

Ethical considerations: The study was approved by the Nicolae Testemițanu SUMPh Ethics Committee (favorable opinion of the Committee for Research Ethics at no.6 of 18.05.2023). Informed consent was waived due to the retrospective design. All data were de-identified and handled according to the Declaration of Helsinki of 1975, as revised in 2000.

Results

Patient characteristics: Among the 1,000 COVID-19 survivors, the median age was 66 years (22-89; IQR 58-74), and 58% were male. Comorbidities were common: 64% had hypertension, 24% diabetes, and 26% cardiovascular disease. The median Charlson Index was 4 (IQR 3-5). Pre-existing CKD (stages 1-4) was present in 200 patients (20%)-mainly stage 3 (n=142) and stage 4 (n=40). The remaining 800 patients (80%) had no known CKD (eGFR ≥60). AKI occurred in 310 patients (31%), and 55 (5.5%) required acute dialysis. In-hospital mortality during acute COVID-19 was 12.3%, and the 1,000 survivors entered follow-up.

AKI and CKD progression after COVID-19: During a median 12-month follow-up, 180/800 (22.5%) patients without prior developed new CKD stage ≥3, and 120/200 (60%) patients with pre-existing worsened CKD by at least one stage. Conversely, 700 patients (70%) showed no progression. Among those without

Table 1. Baseline characteristics of COVID-19 survivors with vs. without CKD progression

Characteristic	AKI Onset+ (n=300)	No AKI Onset+ (n=700)	p-value
Age, years (median, IQR)	71 (65-78)	62 (55-70)	<0.001[1]
Male sex, %	60%	57%	0.48
Hypertension, %	74%	62%	0.005
Type 2 Diabetes Mellitus, %	27%	21%	0.017
Cardiovascular Disease, %	31%	23%	0.040
Obesity (BMI ≥30), %	29%	26%	0.34
Charlson Comorbidity Index (median)	5 (4-7)	3 (2-5)	<0.0001
Acute COVID-19 AKI, %	45%	25%	<0.0001
ICU care for COVID-19, %	22%	15%	0.008
Baseline CKD present, %	40%	11%	<0.0001

Note: [1] $p<0.001$ by Mann-Whitney U test for age (non-normal distribution). Other p-values by chi-square test or t-test as appropriate.

prior CKD, 77.5% maintained normal renal function, while 40% of patients with CKD remained stable.

The comparison between AKI onset and progressors vs non-progressors (Table 1) summarizes the baseline characteristics and acute illness features of patients who developed CKD and who progressed in CKD status versus those who did not. Patients who experienced post-COVID AKI and CKD progression were significantly older than those who did not progress (median age 71 vs 62 years, $p<0.001$). The progression group also had a higher prevalence of key chronic conditions: hypertension was present in 74% of progressors vs 62% of non-progressors ($p= 0.005$), diabetes in 27% vs 21% ($p=0.017$), and cardiovascular disease in 31% vs 23% ($p=0.04$). The rate of obesity was slightly higher in the progression group (29% vs 26%) but this difference was not statistically significant ($p=0.34$). Comorbidity burden, as quantified by the Charlson index, was markedly greater in those with CKD progression (median CCI 5 vs 3, $p<0.0001$). A Charlson index >4 (approximately corresponding to having 2 or more significant comorbid conditions) was observed in 58% of progressors, compared to 30% of non-progressors.

Acute COVID-19 course. Severity of the acute illness strongly influenced long-term renal outcomes. AKI occurred in 45% of patients who later developed CKD progression versus 25% of non-progressors ($p<0.0001$). ICU admission was also more common among progressors (22% vs 15%, $p=0.008$). These findings indicate that severe acute disease-particularly AKI-predisposes patients to chronic renal impairment, with older and more comorbid individuals being most affected.

Outcomes: mortality and renal replacement therapy. Overall mortality during follow-up was 8.6% (86/1000), but differed sharply by renal trajectory. Patients with CKD progression had 15.0% mortality (45/300) versus 5.9% (41/700) in non-progressors ($p<0.001$). Baseline CKD was an even stronger determinant: mortality was 20% (40/200) in those with pre-existing CKD vs 5.8% (46/800) without it ($p<0.0001$), representing a ~3.5-fold higher risk. After adjustment, baseline CKD remained an independent predictor (HR ~2.5, 95% CI 1.8-3.5). Most deaths in CKD patients were due to renal failure, cardiovascular events, or infections.

Chronic dialysis was initiated in 27 patients (2.7%), all from the progression group (15 with advanced baseline CKD; 12 with new ESKD after severe AKI). No non-progressors required dialysis. Renal survival curves confirmed significantly worse outcomes in progressors ($p<0.0001$).

Independent predictors of CKD progression. Multivariate analysis identified baseline CKD as the strongest predictor (OR ≈3.8; 95% CI 2.7-5.4; $p<0.0001$). Age increased risk (OR ~1.5 per decade). Significant comorbidity predictors included hypertension (OR ~1.6; $p=0.01$), cardiovascular disease (OR ~1.4; $p=0.04$), and poorly controlled diabetes (OR ~1.5; $p=0.03$), particularly with obesity (OR ~2.0). A Charlson index >4 increased risk (OR ~2.2; $p<0.001$). Sex was not predictive. AKI independently increased the odds of CKD progression (OR ~1.9; 95% CI 1.4-2.6; $p<0.001$).

Independent predictors of mortality. In Cox models, CKD progression predicted mortality (HR ~1.88; $p= 0.004$), but baseline CKD (HR ~2.5; $p<0.001$) and Charlson index (HR ~1.2 per point; $p<0.001$) remained dominant when analyzed together. Advanced age (HR ~1.5 per decade; $p<0.001$) and cardiovascular disease (HR ~1.7; $p=0.01$) also increased mortality risk. Patients with baseline CKD who subsequently worsened had the poorest overall prognosis.

Discussion

In this cohort of 1,000 survivors hospitalized for COVID-19, CKD progression emerged as a frequent long-term outcome, affecting nearly one-third of patients and supporting the concept of "renal long COVID" [5,10]. Older age, hypertension, diabetes, cardiovascular disease, and higher comorbidity burden were strongly associated with renal deterioration, consistent with risk factors described in prior studies [12,18]. These conditions likely exacerbate SARS-CoV-2–induced inflammatory and hemodynamic injury. Younger patients without comorbidities rarely developed CKD [12,22].

Pre-existing CKD had the strongest impact on outcomes: such patients were over 2-3 times more likely to progress and had significantly higher mortality, aligning with evidence that CKD is a major predictor of severe COVID-19 and death [17,18,23]. CKD may reduce physiological reserve and amplify systemic inflammation, contributing to poor recovery.

The high incidence of CKD progression in our study (30% overall; 22.5% new CKD; 60% CKD worsening) fits within the broad range reported in the literature, though somewhat higher than in studies including milder infections. A scoping review noted new CKD in 0.4-45% and progression in 8-49% of post-COVID cohorts [7,10,22]. Our findings likely reflect the severity of illness, as AKI-present in 31% - is a well-known driver of long-term CKD [10,16,23]. AKI nearly doubled the risk of progression.

Importantly, most patients without traditional risk factors remained free of CKD, suggesting that long-term renal injury is concentrated in vulnerable subgroups [7,15]. Some reports found no CKD development in healthier populations [8,11,19], emphasizing the need for targeted follow-up.

Mortality patterns further illustrate this vulnerability: CKD progression correlated with death, but baseline CKD was the dominant predictor, consistent with large epidemiologic studies [8,12,21]. This highlights CKD as both a consequence and a marker of systemic frailty.

Clinically, all hospitalized COVID-19 survivors-especially older, comorbid patients or those with AKI-should undergo post-COVID renal monitoring, as recommended by expert consensus [13,19,20]. Early nephrology referral and optimization of reno-protective strategies (blood pressure and glycemic control, ACEi/ARB use, avoidance of nephrotoxins, consideration of SGLT2 inhibitors) may mitigate progression. Cardiovascular risk reduction is also essential, given shared pathophysiology.

At a public health level, even small increases in CKD incidence after COVID-19 translate into substantial population-level burden. Estimates suggest hundreds of thousands of new CKD cases globally linked to COVID-19. Health systems must prepare through expanded renal care capacity and structured follow-up programs.

Limitations: This single-center retrospective study may be limited for its generalizability. Residual confounding is possible, including effects of treatments, viral variants, or vaccination (not stratified). CKD progression was defined by stage or eGFR decline, potentially missing subtle changes, though sensitivity analysis was consistent. Median follow-up was 12 months, so late-onset CKD may be underdetected. Lack of complete proteinuria data limits assessment of full renal involvement.

Conclusions

COVID-19 can have a profound and lasting impact on the kidneys. In our cohort of the survivors from severe COVID-19, nearly one-third experienced new or worsening CKD in the year following their illness. Older age and high comorbidity burden (notably hypertension, diabetes, and cardiovascular disease) were identified as key risk factors for post-COVID CKD progression, and these patients should be targeted for careful renal follow-up. Pre-existing CKD emerged as a critical determinant of outcomes-patients with baseline kidney impairment are not only more prone to further renal decline after COVID-19 but also suffer higher mortality. COVID-19 survivors with these risk factors represent a vulnerable group in whom early nephrological intervention and risk factor optimization may be lifesaving. Our findings reinforce the need for an integrated post-COVID care strategy that includes monitoring of kidney function, in line with recent recommendations. By recognizing those at greatest risk and managing their kidney health proactively, we can hopefully mitigate the long-term toll of the COVID-19 pandemic on CKD and overall patient well-being.

Acknowledgments and Funding

The authors thank the clinical staff for assistance and all patients for participation. No specific funding was obtained for this study. The results presented in this paper have not been published previously in whole or part, except in abstract form.

Conflict of interest statement. None declared.

References

1. Abdallah E, Al Helal B, Asad R, *et al*. Incidence and outcomes of acute kidney injury in critically Ill patients with coronavirus disease 2019. *Saudi J Kidney Dis Transpl* 2021; 32: 84-91.
2. Ackermann M, Anders HJ, Bilyy R, *et al*. Patients with COVID-19: in the dark-NETs of neutrophils. *Cell Death Differ* 2021; 17: 751-764.
3. Bowe B, Cai M, Xie Y, *et al*. Acute kidney injury in a national cohort of hospitalized us veterans with COVID-19. *Clin J Am Society Nephrol* 2021; 16: 14-25.
4. Al-Aly Z, Bowe B, Xie Y. Long COVID after breakthrough SARS-CoV-2 infection. *Nat Med* 2022; 28: 1461-1467.
5. Atiquzzaman M, Thompson JR, Shao S, *et al*. Long-term effect of COVID-19 infection on kidney function among COVID-19 patients followed in post-COVID-19 recovery clinics in British Columbia. Canada. *Nephrol Dial Transplant* 2023; 38: 2816-2825.
6. Bowles KH, McDonald M, Barron Y, *et al*. Surviving COVID-19 after hospital discharge: symptom, functional, and adverse outcomes of home health recipients. *Ann Intern Med* 2021; 174: 316-325.
7. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med* 2014; 371: 58-66.
8. Cheng Y, Luo R, Wang K, *et al*. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int* 2020; 97: 829-838.
9. Chu CD, McCulloch CE, Banerjee T, *et al*. CKD awareness among us adults by future risk of kidney failure. *Am J Kidney Dis* 2020; 76: 174-183.
10. Coca A, Burballa C, Centellas-Pérez FJ, *et al*. Outcomes of COVID-19 Among Hospitalized Patients with Non-dialysis CKD. *Front Med (Lausanne)* 2020; 7: 615312.
11. Dell'Aquila K, Lee J, Wang SH, *et al*. Incidence, characteristics, risk factors and outcomes of diabetic ketoacidosis in COVID-19 patients: Comparison with influenza and pre-pandemic data. *Diabetes Obes Metab* 2023; 25(9): 2482-2494.
12. Eligulashvili A, Darrell M, Miller C, *et al*. COVID-19 Patients in the COVID-19 Recovery and Engagement (CORE) Clinics in the Bronx. *Diagnostics (Basel)* 2022; 13: 119.
13. Eriksson KE, Campoccia-Jalde F, Rysz S, Rimes-Stigare C. Continuous renal replacement therapy in intensive care patients with COVID-19; survival and renal recovery. *J Crit Care* 2021; 64: 125-130.
14. Farouk SS, Fiaccadori E, Cravedi P, Campbell KN. COVID-19 and the kidney: what we think we know so far and what we don't. *J Nephrol* 2020; 33: 1213-1218.
15. Flash MJE, Johnson SF, Tiako MJN, *et al*. Disparities in post-intensive care syndrome during the COVID-19 pandemic: challenges and solutions. *NEJM Catalyst* 2020; 7(8): e54-e55.
16. Gok M, Cetinkaya H, Kandemir T,*et al*. Chronic kidney disease predicts poor outcomes of COVID-19 patients. *Int Urol Nephrol* 2021; 53: 1891-1898.
17. Henry BM, Lippi G. Chronic kidney disease is associated with severe coronavirus disease 2019 (COVID-19) infection. *Int Urol Nephrol* 2020; 52: 1193-1194.

18. Hittesdorf E, Panzer O, Wang D, *et al*. Mortality and renal outcomes of patients with severe COVID-19 treated in a provisional intensive care unit. *J Crit Care* 2021; 62: 172-175.
19. Lu JY, Ho SL, Buczek A, Fleysher R,*et al*. Clinical predictors of recovery of COVID-19 associated-abnormal liver function test 2 months after hospital discharge. *Sci Rep* 2022; 12: 17972.
20. Strohbehn IA, Zhao S, Seethapathy H, *et al*. Acute kidney injury incidence, recovery, and long-term kidney outcomes among hospitalized patients with COVID-19 and influenza. *Kidney Int Rep*. 2021; 6(10):2565-2574.
21. Tan BWL, Tan BWQ, Tan ALM, *et al*. Long-term kidney function recovery and mortality after COVID-19-associated acute kidney injury: An international multi-centre observational cohort study. *EClinicalMedicine* 2023; 55: 101724.
22. RăzlogT, Russu E, Alexa Z, *et al*. Manifestations of kidney involvement in COVID-19 patients and progression to chronic kidney disease. *Mold J Health Sci* 2024; 1(11): 11-18.
23. Valeri AM, Robbins-Juarez SY, Stevens JS, *et al*. Presentation and outcomes of patients with ESKD and COVID-19. *J Am Soc Nephrol* 2020; 31: 1409-1415.

BANTAO Journal 2025; 23(2): 36-39

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Case reports and literature review

A Modest Experience in the Treatment of Membranous Nephropathy with Classical and Alternative Medications

Biser Borisov and Svilena Aleksandrova

Department of Nephrology, Faculty of Medicine, Medical University, Pleven, Bulgaria

Abstract

Introduction. Membranous nephropathy (MN) is the most common morphological finding found in cases of nephrotic syndrome in adults. Etiologically it is divided into primary (PMN) and secondary (SMN). Treatment of patients with MN is carried out with corticosteroids, immunosuppressants, monoclonal antibodies and others, depending on the determined degree of risk in the respective patients.

Case reports. We describe two cases from clinical practice with biopsy established MN, as PMN, in which we carried out treatment with intermittent "pulses" of glucocorticoids and/or cyclophosphamide with simultaneous administration of medications with nephroprotective and/or anti-inflammatory effects-SGLT2 inhibitors and finerenone.

Results. The patients were followed up for six months. During this period, remission of the main manifestations of the disease was achieved in all patients without any deterioration of the renal function. Subsequent observation and non-pathogenetic treatment in the next six months also showed no disease activity.

Conclusion. The excellent results we have reported in these patients, in our opinion, are an evidence that the individual approach to treatment does not contradict the accepted rules of Good Clinical Ppractice, but often complements them well under the appropriate conditions.

Keywords: membranous nephropathy, nephrotic syndrome, corticosteroids, immunosuppressants, alternative medications, SGLT2 inhibitors, Finerenone

Introduction

Membranous nephropathy (MN), also known as membranous glomerulonephritis, is one of the most frequently detected morphologically chronic glomerulonephritis, clinically manifested by nephrotic syndrome-massive proteinuria (>3.5 g/day), hypo- and dysproteinemia, and edema of nephrotic-type. The etiology can be primary (75-80%) and secondary (20-25%), but remains unknown [1]. The role of viral and bacterial infections, environmental pollution, and genetic predisposition is discussed. It is believed that people of European and East Asian descent are genetically predisposed to the development of this nephropathy due to defects in two non-HLA loci that are transcriptional regulators of inflammation [2-6]. The diagnosis, as in all cases of unknown nephropathies, is proven only by renal biopsy. Differentiating the primary from the secondary form requires numerous additional studies and even then, it may not be proven definitively.

Case 1.

A 61-year-old Caucasian male with a history of long-term arterial hypertension presented with a constellation of nephrotic syndrome: pronounced edema of the lower extremities of the nephrotic type with proteinuria of 11.4 g/l, reduced total protein levels of 35.2 g/l, and albumin of 17.8 g/l, with e-GFR of 81 ml/min/1.73 m^2
Serological markers for hepatitis B and C were negative, as well as the immunological markers for systemic lupus in two consecutive measurements.
Kidney biopsy was consistent of Membranous nephropathy of GN, class II, with abundant deposits of IgA, IgG, IgM, C3, C1q.
After biopsy clarification, the following treatment was started (Table 1):

Table 1. The medications used for treatment were cyclophosphamide (CYC); glucocorticoids (GC); Sodium-glucose transport inhibitors 2 (SGLT2)

	1st month	2nd month	3rd month	4th month	5th month	6th month
CYC	+	+	+	+	+	+
GC	+	+			+	
SGLT2	+	+	+	+	+	+

Correspondence to: Svilena Aleksandrova, Department of Nephrology, Faculty of Medicine, Medical University, Pleven, Bulgaria. UMHAT "Dr. G. Stranski", Department of Nephrology, 5800 Pleven, Bulgaria; E-mail: svilena.aleksandrova98@gmail.com

The main treatment included: Cyclophosphamide from 1st to 6th monthly pulse doses of 500 mg i.v., Methylprednisolone at 1st and 2nd month with pulse doses of 500 mg/3 days in row i.v., and SGLT-2 inhibitor x 10mg/daily.
Symptomatic treatment also included olmesartan/amlodipine, diuretics, and supplementation for protein loss.
After the 6-th month, the following changes were found: lack of edema in the lower extremities, reduction of body weight by 32%, decrease in proteinuria to 0.9 g/L, increase in total protein to 59.2 g/L, and albumin to 35.4 g/L, and increase of e-GFR to 100 ml/min/1.73 m^2.

Case 2.

A 41-year-old man, Caucasian race, arterial hypertension with a 5-year history, was admitted with a constellation of nephrotic syndrome with mild edema in the lower extremities of nephrotic type, proteinuria of 4.91 g/L, total protein of 54.6 g/l, albumin was 29.4 g/l, and e-GFR - 112 ml/min/1.73 m^2.
In addition, there were negative serological markers for hepatitis B and C, and negative immunological markers for systemic lupus, determined twice.
Kidney biopsy showed membranous nephropathy, class II, with abundant deposits of IgA, IgG, IgM, C3, C4, C1q.
We conducted the following treatment on this patient (Table 2):

Table 2. Main medications used for treatment by month (CYC - cyclophosphamide; GC - glucocorticoids)

	1st month	2nd month	3rd month	4th month	5th month	6th month
CYC	+	+	+	+	+	+
GC	+	+				
Finerenone	+	+	+	+	+	+

The main treatment included: Cyclophosphamide from 1st to 6th monthly pulse doses of 500 mg i.v., Methylprednisolone at 1st and 2nd month with pulse doses of 500 mg/3 days in row i.v., and Finerenone x 10mg/daily.
Symptomatic treatment also included olmesartan/amlodipine, diuretics, and protein loss supplementation.
The follow up after 6 months revealed an absence of edema in the lower extremities, the proteinuria was reduced to 0.64 g/l, and total protein increased to 71.5 g/l, and albumins to 41.1 g/l, while e-GFR increased to 94 ml/min/1.73 m^2**.**

Discussion

Membranous nephropathy is a heterogeneous disease, occurring either in the absence of an established cause (80% of cases), or in association with clinical conditions, such as infections (hepatitis B), lupus erythematosus, neoplasm or any drug intoxication, thus defining the so-called primary and secondary membranous nephropathy, respectively.
The search for markers for identification of MN is associated with the discovery of the neutral endopeptidase (NEP) antigen and the phospholipase-A2 receptor antigen (PLA2R). After 2019, the following biomarkers are used to differentiate the underlying cause: exostosins 1/2 (EXT1/2)-a marker for lupus nephropathy class V; neural epidermal growth factor-like 1 protein (NELL-1)-a major biomarker in "primary" and neoplastic MN; semaphorin 3B (Sema3B)-the most common biomarker in childhood; neural cell adhesion molecule 1 (NCAM1)-a marker for lupus nephropathy class V [7].
Despite the extensive morphological findings in our patients, we did not find any positive signs of paraneoplastic nephropathy, and triple standard immunological studies for systemic lupus remained negative. We lack laboratory facilities for testing new and specific markers - PLA2R, NELL-1, NCAM1, which limits the objectivity of diagnosis in these cases.
Currently, the approach to treating patients with MN is highly individualized, with experts recommending a conservative regimen tailored to the specific complaints of each patient, clinical manifestations and level of proteinuria.
Of the non-pharmacological factors, the following ones are important: Increased physical activity; Limited salt intake - up to 2.0 g/day; Limited protein intake - 0.8-1 g/kg/day [8].
The first choice in the presence of hypertension is the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), relying on their protective effect on the kidney, associated with the reduction of hyperfiltration, stabilization of the basement membrane and their influence on the transport of molecules across the renal mesangium.
Protein supplementation is also used in the presence of hypoalbuminemia, usually combined with diuretic therapy.
Hyperlipidemia in nephrotic syndrome is a secondary phenomenon, the result of a defective compensatory mechanism and its presence indicates that it is a prolonged nephrotic syndrome. Once it occurs, however, hyperlipidemia adversely affects renal function and the performance of all major systems in the body, for which it is indicated for treatment with statins.
Increased thrombotic risk correlates with the degree of hypoproteinemia and requires the use of at least aspirin, and in more severe cases-low molecular weight heparins and indirect anticoagulants for a prolonged period [9-11].

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines from 2021 define four risk categories for classifying MN: low, intermediate, high and very high risk.
The most commonly used treatment regimens are: C. Ponticelli regimen-alternating GC and Cyclophosphamide; Calcineurin inhibitors; Rituximab-CD20-antibody therapy.
In patients with intermediate risk-rituximab or calcineurin inhibitor with or without glucocorticoids. For those with high risk-rituximab or cyclophosphamide, alternating with glucocorticoids, or calcineurin inhibitor with rituximab. For very high-risk patients, the recommended treatment includes the use of cyclophosphamide and glucocorticoids [12].
In the cases described by us, the first meets the criteria for a high-risk patient, and the second-for a moderate-high risk. Our patients were not able to purchase either calcineurin inhibitor or Rituximab at their own expense, and the use of these drugs in MN is Off-label. For this reason, we started treatment with CYC and GC-only "pulse", once a month, without the use of conventional medication, as in the classic scheme of C. Ponticelli.
The patients have been followed for 12 months after the described specific therapy, and after the 6th month, we have not used either CYC or GC in both patients, but only SGLT2 inhibitor and antihypertensive therapy with ARB. During the follow-up period, there was no significant change in proteinuria values and renal function, expressed by e-GFR.
SGLT2 inhibitors were initially indicated to improve glycemic control in type 2 diabetes. It has been established that SGLT2 inhibitors exert nephroprotective effects beyond glucose regulation and reduction of intraglomerular pressure through tubuloglomerular feedback. Inhibition of SGLT2 leads to an initial decrease in eGFR in patients without diabetes, which stabilizes over time. Studies of the effect of SGLT2 inhibitors (DAPA-CKD, EMPA-KIDNEY) have reduced proteinuria by 32% in patients with MN [13,14].
The mineralocorticoid receptor (MR) is a transcription factor that is expressed in various tissues: kidneys, heart, blood vessels, etc. The role of MR is well expressed in the distal nephron on aldosterone-sensitive renal epithelial cells expressing 11b-hydroxysteroid dehydrogenase type 2. In these cells, MR activation is primarily associated with the regulation of blood pressure and sodium retention, but the MR receptor is also expressed in non-epithelial renal cells, in several other tissues, including adipocytes, vascular smooth muscle cells (VSMCs), immune cells, cardiomyocytes, where it may participate in the regulation of their growth. MR can promote fibrosis and inflammation, leading to progression of renal and cardiovascular disease.
MR antagonists are a relatively new class of drugs currently being tested in patients with type 2 diabetes. Phase II and III clinical trials (ARTS, ARTS-DN, ARTS-HF, FIDELIO-DKD, FIGARO-DKD, FIDELITY) have shown dose-dependent reductions in albuminuria with Finerenone and adverse events profile similar to placebo [15,16].
In addition, studies investigating the effects of the combination of Finerenone and sodium-glucose cotransporter 2 (SGLT2) inhibitors (empagliflozin) in chronic kidney disease (CKD) and T2DM (CONFIDENCE) and the selective MR modulator AZD9977 with another SGLT2 inhibitor (dapagliflozin) in HF and T2DM (MIRACLE) aim to expand treatment options. Although SGLT-2 inhibitors have been shown to reduce the risk of hyperkalemia in FIDELIO-DKD and potentially reduce the incidence of new-onset HF in FIGARO-DKD, further studies are needed. To date, the evidence for the beneficial effects of Finerenone across the spectrum of cardiorenal disease is based only to the results of studies conducted in patients with type 2 diabetes, while clinical trials of Finerenone in patients with nondiabetic kidney disease are ongoing. Finally, nonsteroidal MRAs have significant potential as key therapeutic targets across the spectrum of cardiorenal disease [17,18].
The prognosis of MN is: 1/3 of patients reach spontaneous remission, 1/3 achieve partial remission with the development of stable CKD and 1/3 are therapeutically resistant and reach relatively quickly terminal renal failure and the need for renal replacement therapy [19].
Despite the great successes in unraveling the idiopathic forms of the disease and the use of various new molecules with activity against CD19/CD20 rituximab, obinutuzumab, ocrelizumab and ofatumumab, calcineurin inhibitors and others, there is still a lack of convincing data on a serious reduction in resistant cases [20-23].

Conclusion

The reported cases are only proof that, based on established therapeutic models, we can seek individual solutions for our patients with the help of medications that are not yet approved for the treatment of one or another nephropathy, but have a positive effect on the progression of CKD through different mechanisms.

Conflict of interest statement. None declared.

References

1. Alok A, Yadav A. Membranous Nephropathy. [Updated 2023 Jun 5]. In: StatPearls [Internet]. *Treasure Island (FL): StatPearls Publishing* 2025 Jan-. [PubMed - https://pubmed.ncbi.nlm.nih.gov/32644595/].

2. Ponticelli C, Glassock RJ. Glomerular diseases: Membranous nephropathy-A modern view. *Clin J Am Soc Nephrol* 2014; 9: 609.
3. Couser WG. Primary Membranous Nephropathy. *Clin J Am Soc Nephrol* 2017; 7: 983-997.
4. Gupta S, Köttgen A, Hoxha E, *et al*. Genetics of membranous nephropathy. *Nephrol Dial Transplant* 2018; 33: 1493-1502.
5. Kamyshova ES, Bobkova IN, Gorelova IA, *et al*. Genetic determinants of the development and course of membranous nephropathy. *Ter Arkhiv* 2018; 90: 105-111.
6. Xie J, Liu L, Mladkova N, *et al*. The genetic architecture of membranous nephropathy and its potential to improve non-invasive diagnosis. *Nat Commun* 2020; 11: 1600.
7. Ronco P, Debiec H. Membranous nephropathy: current understanding of various causes in light of new target antigens. *Curr Opin Nephrol Hypertens* 2021; 30(3): 287-293.
8. Wang M, Yang J, Fang X, *et al*. Membranous nephropathy: pathogenesis and treatments. *MedComm (2020)* 2024; 5(7): e614.
9. Geddes CC, Cattran DC. The treatment of idiopathic membranous nephropathy. *Semin Nephrol* 2000; 20(3): 299-308.
10. Duffy M, Jain S, Harrell N, *et al*. Albumin and furosemide combination for management of edema in nephrotic syndrome: a review of clinical studies. *Cells* 2015; 4(4): 622-630.
11. Hofstra JM, Wetzels JFM. Should aspirin be used for primary prevention of thrombotic events in patients with membranous nephropathy? *Kidney Int* 2016; 89(5): 981-983.
12. Kidney Disease: improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int* 2021; 100(4S): S1-S276.
13. Del Vecchio L, Peiti S, Pucci Bella G, Locatelli, F. SGLT2 Inhibitors in Glomerulonephritis: Beyond Nephroprotection? *J Clin Med* 2025; 14: 3533.
14. Chertow GM, Heerspink HL, Mark PB, *et al*. Effects of Dapagliflozin in Patients with Membranous Nephropathy. *Glomerular Dis* 2024; 4(1): 137-145.
15. Filippatos G, Anker SD, Agarwal R, *et al*. Finerenone reduces risk of incident heart failure in patients with chronic kidney disease and type 2 diabetes: analyses from the FIGARO-DKD trial. *Circulation* 2022; 145: 437-447.
16. Di Lullo L, Lavalle C, Scatena A, *et al*. Questions and Answers-The Four Fundamental Arguments on the New-Born Promising Non-Steroidal Mineralocorticoid Receptor Antagonist. *J Clin Med* 2023;12(12): 3992.
17. Kolkhof P, Hartmann E, Freyberger A, *et al*. Effects of Finerenone combined with empagliflozin in a model of hypertension-induced end-organ damage. *Am J Nephrol* 2021; 52: 642-652.
18. Rebelos E, Tentolouris N. Complementary actions of Finerenone and SGLT2-i on renal outcomes? An urgent need for more information. *Nephrology (Carlton)* 2022; 27(12): 915-916.
19. Couser WG. Primary Membranous Nephropathy. *Clin J Am Soc Nephrol* 2017; 12(6): 983-997.
20. Fleig SV, Konen FF, Schröder C, *et al*. Long-term b cell depletion associates with regeneration of kidney function. *Immun Inflammation Dis* 2021; 9(4): 1479-1488.
21. Wei SY, Wang YX, Li JS, *et al*. Serum anti-PLA2R antibody predicts treatment outcome in idiopathic membranous nephropathy. *Am J Nephro* 2016; 43(2): 129-1240.
22. Teisseyre M, Cremoni M, Boyer-Suavet S, *et al*. Advances in the Management of Primary Membranous Nephropathy and Rituximab-Refractory Membranous Nephropathy. *Front Immunol* 2022; 13: 859419.
23. Shah M, DeLaat A, Cavanaugh C. Treatment of membranous nephropathy: Perspectives on current and future therapies. *Front Nephrol* 2023; 3:1110355.

BANTAO Journal 2025; 23(2): 40-42

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Case report

The Association Between Statin Drugs and Kidney Injury

Stefan Filipovski, Blerta Dzemaili[1], Fortim Isa[2], Muhammed Saidi[1], Zoran Janevski[1], Zvezdana Petronijevic[1], Pavlina Dzekova Vidimliski[1] and Vesna Ristovska[1]

[1]University Clinic for Nephrology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, [2]Public health institute – Specialized hospital for Nephrology, Struga, Republic of North Macedonia

Abstract

Introduction. Statins are widely prescribed lipid-lowering agents that significantly reduce cardiovascular morbidity and mortality, They are frequently prescribed as first-line drugs for the primary and secondary prevention of coronary, cerebral and peripheral ischemic vascular events. Although effective and tolerated by most patients, myotoxicity is a rare but well-documented adverse effect of all statins that usually occurs within weeks or months. The aim of this presentation is to review the pathophysiological mechanisms and diagnosis of statin associated myotoxicity, focusing on the most effective strategies for statin intolerance clinical management. Hence, we present two different cases of statin induced rhabdomyolysis with different treatment, one with help from medium cut off (MCO) dialyzer, and the other with conservative approach with a lot of fluids and diuretic stimulation.
Case reports. The first case is a 68 years old male, on chronic therapy with atorvastatin proposed from cardiologist after having heart problems three years ago. One month before the hospital admission, the patient had elevated creatine kinase and myoglobin, and statin was removed from the therapy. The initial myoglobin level was 700ng/ml and creatine kinase 1500U/L. An excessive fluid parenteral administration was initiated with over 3000ml with an additional oral intake. While under hospital treatment, 24h diuresis was measured between 2300ml up to 4500ml. On the day of discharge, his creatine kinase was 300U/L, myoglobin 200ng/ml and serum creatinine was 138μmol/L. He was instructed for a regular checkup thereafter.
The second case was also a 69 years old male, with chronic kidney disease (CKD) and congestive heart failure with 35% EF. A week before admission the patient has felt problems with walking, pain in the muscles and on three days before the actual hospital admission he was treated in the nearby hospital and transferred because of an acute worsening of the CKD for further treatment. At the admission, the creatine kinase level was 57904U/L.
Because of the highly elevated waste products (urea and creatinine) a treatment with hemodialysis was initiated. A total of 11 hemodialysis was performed, and in 7 of them MCO dialyzer was used. Creatinine kinase level has declined up to 243 U/L. No proper creatine decline has been managed and the patient was discharged with the need for chronic hemodialysis treatment with regular checkups for eventual discharge from the chronic hemodialysis program (CHDP).
Conclusion. We can say that the choice of statin in patients with kidney disease is complex and depends on specific risk factors. This fact is important for choosing the right treatment in these patients. The data and conclusions may help guide future clinical practice and research in this area.

Key words: statins therapy, rhabdomyolysis, kidney injury, medium cut off membrane, myoglobin

Introduction

Statins are widely prescribed lipid-lowering agents that significantly reduce cardiovascular morbidity and mortality. They are competitive inhibitors of HMG-CoA-reductase (3-hydroxy-3-methylglutaryl-CoA reductase) and thereby reduce cholesterol synthesis, so they are frequently prescribed as first-line drugs for the primary and secondary prevention of coronary, cerebral and peripheral ischemic vascular events [1-3]. Although effective and tolerated by most patients, myotoxicity is a rare but well-documented adverse effect of all statins that usually occurs within weeks or months. However, their use is occasionally associated with adverse muscular effects, ranging from mild myalgia to severe rhabdomyolysis. Statin-induced rhabdomyolysis is a rare but potentially life-threatening condition characterized by muscle breakdown, elevated creatine kinase levels, and risk of acute kidney injury. The mechanism of statin-associated myotoxicity is not entirely certain, but toxicity is dose-dependent and several risk factors have been identified. Indeed, any

Correspondence to: Vesna Ristovska, University Clinic for Nephrology, 1000 Skopje, R. N. Macedonia; E-mail: v.ristovska@yahoo.com

clinical case of statin-induced myotoxicity can be seen as multifactorial [3-5].
The aim of this presentation is to give an update on pathophysiological mechanisms and diagnosis of statin associated myotoxicity, focusing on the most effective strategies for statin intolerance clinical management, including new emerging alternative therapies. This review aims to improve diagnostic and therapeutic approaches in order to increase statin adherence and reduce cardiovascular events [5].

Case report

Here in, we present two different cases of statin induced rhabdomyolysis with different treatment, one with help from medium cut off (MCO) dialyzer, and the other with a conservative approach with a lot of fluids and diuretic stimulation.

Case 1

We report a case of 68 years old male, on chronic therapy with atorvastatin proposed from cardiologist after having heart problems three years ago.
One month before the hospital admission, the patient had an elevated creatine kinase and myoglobin, and statin was removed from therapy. It was given parenteral fluids and vitamin therapy four days through daily visits in hospital. On the second control one month after daily hospital treatment creatine kinase and myoglobin were insignificantly depleted showing no regression and decision was made for hospital treatment. On the admission day the myoglobin level was 700ng/ml and creatine kinase 1500U/L. The other laboratory findings were as follows: hemoglobin 109..112g/L, erythrocytes 3.39..3,49, hematocrit 0.31..0,32, BUN 5.7..4,7 mmol/L, creatinine 138..134umol/L, creatine kinase 2028..1087U/L, myoglobin 229..206ng/ml, CRP 1.7..2.9.
An excessive fluid parenteral administration was initiated with over 3000ml with an additional oral intake. Diuretics were used only the first day and during the hospitalization the 24h diuresis was measured between 2300ml up to 4500ml. On the day of discharge, his creatine kinase was 300U/L, and myoglobin 200ng/ml. Serum creatinine was 138µmol/L. He was instructed for a regular checkup afterwards. regular checkup thereafter.

Case 2

The second case was also a 69 years old male with chronic kidney disease (CKD) and congestive heart failure with 35% EF. A week before admission the patient has felt problems with walking, pain in the muscles and on three days before the actual hospital admission he was treated in the nearby hospital and transferred because of an acute worsening of the CKD for further treatment. At the admission, the creatine kinase level was 57904U/L. The other laboratory findings were as follows: hemoglobin 119..71..91g/L, erythrocytes 3.82..2.26..2.88, hematocrit 0.35..0.22..0.26, BUN 30.8..5.9..8.3mmol/L, creatinine 762..329..573µmol/L, creatine kinase 7904..1089..243U/L, myoglobin 615..1071..362 ng/ml, CRP 1.1..22..17.1, AST 1137..62U/L, ALT 693..152U/L.
Because of the highly elevated waste products (urea and creatinine) a treatment with hemodialysis was initiated. A total of 11 hemodialysis was performed, and in 7 of them MCO dialyzer was used. Creatinine kinase level has declined up to 243 U/L. No proper creatine decline has been managed and the patient was discharged with the need for chronic hemodialysis treatment with regular checkups for eventual discharge from the chronic hemodialysis program (CHDP). Urine output has slowly corrected from 200ml/24h up to 1250ml/24h. No other direct cause for the rhabdomyolysis has been confirmed.

Discussion

Understanding the risk factors, clinical presentation, and management of acute kidney injury (AKI) is essential for clinicians to balance the benefits of statin therapy with patient safety. Here we present two case reports treated at our clinic, in one case with the rare use of specific MCO dialyzer and a positive clinical outcome. The patients can rapidly develop severe rhabdomyolysis associated with rosuvastatin therapy while suffering from AKI. Although we were not able to obtain rosuvastatin plasma levels, even without such data, according to the standard semiquantitative causality assessment, rosuvastatin could have been classified as the "probable" cause of rhabdomyolysis in our patient [4].
Statins are generally safe for patients with normal kidney function, but it carries an increased risk of kidney-related side effects, including proteinuria and hematuria, especially at high doses and for people with pre-existing kidney disease. Dosage adjustments are necessary for patients with severe CKD [6,7].
While all statins can affect the kidneys, rosuvastatin has shown a slightly higher risk of kidney issues compared to atorvastatin, with risks increasing with higher doses. An increase in protein (proteinuria) and blood (hematuria) in the urine was observed in clinical trials, particularly with higher dosages. These effects are often temporary and generally do not lead to a decline in overall kidney function.
Our patients have both proteinuria and hematuria, but after they stopped therapy with statins, the urine status was normalized. Some studies published in the Journal of the American Society of Nephrology found that rosuvastatin users had a 15% higher risk of kidney failure requiring replacement therapy (dialysis or transplantation) compared to those taking atorvastatin.

In rare cases, the statin side effect rhabdomyolysis (muscle breakdown) can lead to severe kidney damage or AKI. This risk is higher in individuals with pre-existing kidney problems.

High-dose rosuvastatin has been linked to renal tubular toxicity, a non-rhabdomyolysis-related injury to the kidney's filtering tubules [8,9].

The prescribing guidelines for rosuvastatin emphasize extra caution when treating patients with existing kidney issues. For patients with severe CKD, defined as a creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR) below 30 mL/min, the dose should be started at 5 mg and does not exceed 10 mg daily [10,11].

Patients with an eGFR below 30 have a significantly higher risk of proteinuria and hematuria when taking rosuvastatin compared to those with normal kidney function. Research suggests that other statins may be safer for kidney health, though studies have mixed results [12,13].

A large 2022 observational study comparing rosuvastatin to atorvastatin showed that rosuvastatin was associated with a higher risk of kidney harm, particularly at higher doses [6].

Atorvastatin seems to have a renoprotective effect. In one study, high-dose atorvastatin appeared to have more protective effects on the kidneys compared to high-dose rosuvastatin. Despite some comparative differences, statins as a class have been shown to have overall renoprotective effects and are important for managing cardiovascular risk in patients with CKD [10].

The choice of statin in patients with kidney disease is complex and depends on specific risk factors. A large percentage of patients on lipid lowering therapies have CKD, and data regarding renal outcomes associated with high doses of statins in this population are limited. We found that nearly half of patients with CKD are on inappropriately high doses of rosuvastatin when considering their kidney function. Further research into long term outcomes and statin dosing in this patient population is needed [14,15].

Conclusion

This case report provides important clinical insights into the management of statin-induced rhabdomyolysis and emphasizes the need for personalized approaches in statin therapy, especially in patients with underlying kidney conditions. The choice of statin in patients with kidney disease is complex and depends on specific risk factors. This fact is important for choosing the right treatment in these patients. The data and conclusions may help guide future clinical practice and research in this area.

Conflict of interest statement. None declared.

References

1. Baigent C, Keech A, Kearney PM. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005; 366: 1267-1278.
2. Niedrig DF, Pyra M, Roger Lussman R, *et al*. Rosuvastatin-induced rhabdomyolysis: case report and call for proactive multifactorial risk assessment and preventive management of statin therapy in high-risk patients *Eur J Hosp Pharm* 2024; 31(3): 281-284.
3. Jeeyavudeen MS, Pappachan JM, Arunagirinathan G. Statin-related muscle toxicity: an evidence-based review. *Touch REV Endocrinol* 2022; 18: 89-95.
4. Turner RM, Pirmohamed M. Statin-related myotoxicity: a comprehensive review of pharmacokinetic, pharmacogenomic and muscle components. *J Clin Med* 2019; 9: 22.
5. Vinci P, Panizon E, Tosoni LM, *et al*. Statin-associated myopathy: emphasis on mechanisms and targeted therapy. *Int J Mol Sci* 2021; 22: 11687.
6. Shin JI, Fine DM, Sang Y, Surapaneni A, Dunning SC, Inker LA, Nolin TD, Chang AR, Grams ME. Association of Rosuvastatin Use with Risk of Hematuria and Proteinuria. *J Am Soc Nephrol*. 2022; 33(9):1767-1777.
7. Leelaviwat N, Mekraksakit P, Del Rio-Pertuz G, *et al*. Atorvastatin vs. Rosuvastatin for Contrast-Induced Nephropathy Prevention in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention: A Meta-Analysis of Randomized Controlled Trials and Propensity-Score Matching. *J Am Soc Nephrol* 33(11S):p 353.
8. Zipes DP, Zvaifler NJ, Glassock RJ, *et al*. Rosuvastatin: an independent analysis of risks and benefits. *Med Gen Med* 2006; 8(2):73.
9. McKenney JM. Efficacy and safety of rosuvastatin in treatment of dyslipidemia. *Am J Health Syst Ph*arm 2005; 62(10): 1033-1047.
10. Jones PH, Davidson MH, Stein EA, *et al*. STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol* 2003; 92: 152-160.
11. Zitelny E, Hickey R, Sanghavi M. The Right Dose for the Right Patient - High Intensity Rosuvastatin Dosing in Patients With Chronic Kidney Disease. *Circulation* 2003; 147(Suppl_1): p628.
12. Ward FL, John R, Bargman JM, McQuillan RF. Renal Tubular Toxicity Associated With Rosuvastatin Therapy. *Am J Kidney Dis* 2017; 69(3): 473-476.
13. Ram R, Swarnalatha G, Ramesh V, *et al*. Rhabdomyolysis induced acute renal failure secondary to statins. *Indian J Nephrol* 2013; 23(3): 211-213.
14. Kursat S, Alici T, Colak HB. A case of rhabdomyolysis induced acute renal failure secondary to statin-fibrate-derivative combination and occult hypothyroidism. *Clin Nephrol* 2005; 64: 391-393.
15. Magee CN, Medani SA, Leavey SF, Conlon PJ, Clarkson MR. Severe rhabdomyolysis as a consequence of the interaction of fusidic acid and atorvastatin. Am J Kidney Dis. 2010; 56(5):e11-5.

BANTAO Journal 2025; 23(2): 43-45

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Case Report

Lupus Nephritis in a Postpartum Patient - Case Report

Muhammed Saidi, Sabir Sulejman, Ardijan Memeti, Stefan Filipovski, Zoran Janevski and Vesna Ristovska

University Clinic for Nephrology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, Republic of North Macedonia

Abstract

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disorder characterized by autoantibody production and immune complex-mediated organ damage. The predominant clinical signs include fatigue, fever, weight loss, arthritis, pericarditis, anemia, and pulmonary complications. Diagnosing SLE requires a combination of clinical evaluations and laboratory testing, including antinuclear antibodies and anti-double-stranded DNA antibodies, among others. Lupus nephritis is a serious manifestation of SLE and is particularly challenging during pregnancy and the post-partum period.

We present a case of a previously healthy woman, who developed severe proteinuria, hypertension, and extrarenal lupus manifestations, eight weeks after delivery. Laboratory and immunological findings confirmed new-onset SLE. Renal biopsy established the diagnosis of lupus nephritis. The patient was treated with high-dose corticosteroids, cyclophosphamide, and therapeutic plasmapheresis, resulting in significant clinical and biochemical improvement. This case highlights the importance of an early recognition of lupus nephritis in the post-partum period, when immune rebound phenomenon may precipitate autoimmune activation.

In conclusion, we can say that the early recognition of lupus nephritis in the post-partum period is crucial for the treatment of the lupus nephritis. This patient achieved complete clinical remission following immunosuppressive therapy and continues under nephrology follow-up due to risk of relapse.

Keywords: systemic lupus erythematosus, lupus nephritis, post-partum, renal biopsy, cyclophosphamide, plasmapheresis

Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disorder characterized by autoantibody production and immune complex–mediated organ damage [1,2]. It predominantly affects young women and is more common in Black, Hispanic, and Asian populations. However, its onset involves a complex interplay of genetic predispositions, environmental stimuli, hormonal factors, and immune system abnormalities [1,2]. The predominant clinical signs include fatigue, fever, weight loss, arthritis, pericarditis, anemia, and pulmonary complications [2,3]. Diagnosing SLE requires a combination of clinical evaluations and laboratory testing [2,4], including antinuclear antibodies and anti-double-stranded DNA antibodies, among others [4]. Renal involvement occurs in approximately 50% of patients and typically develops within the first five years after diagnosis [3,5,6]. Lupus nephritis must be considered in patients presenting with unexplained proteinuria, hematuria, or renal dysfunction-even when SLE has not been previously identified. The post-partum period is a known trigger for autoimmune disease exacerbations [7] due to the immunological rebound following pregnancy-related immune modulation. Herein, we present a case of a patient with hypertension during pregnancy and diagnosis of SLE in the post-partum period.

Case Presentation

A previously healthy woman, gravida 2 para 1, developed elevated blood pressure at six weeks of gestation during her second pregnancy and was started on methyldopa. She delivered a healthy infant, but post-partum she continued to experience persistent hypertension and progressive bilateral lower-extremity edema. Eight weeks after delivery, she was presented for nephrology evaluation. Antihypertensive therapy was switched to nifedipine 20 mg. Because of bacteriuria, ciprofloxacin was prescribed.

Laboratory tests revealed proteinuria ++++ and hematuria +++, with serum creatinine 183 μmol/L. The other laboratory findings are presented in Table 1.

Renal ultrasound showed bilaterally enlarged hyperechoic parenchyma with calyceal dilatation, and no lithiasis or obstruction. Due to persistent heavy proteinuria and edema, the patient was hospitalized.

Correspondence to: Vesna Ristovska, University Clinic for Nephrology, 1000 Skopje, R. N. Macedonia; E-mail: v.ristovska@yahoo.com

During hospitalization, echocardiography revealed EF≈43%. The echocardiographic report showed left ventricular systolic and diastolic dysfunction**,** with in-

Table 1. Laboratory findings in patient with SLE and Lupus nephritis during hospitalization

Analyse	Results	References
Erythrocytes	3,9	4.2 – 5.9 ×10¹²/L
Hemoglobin	120	♂ 135–175 · ♀ 120–155 g/L
PLT	203	150 – 400 ×10⁹/L
Glycemia	5.3	3.9 – 5.6 mmol/L (fasting)
Urea	5.5…9.3	2.5 – 7.8 mmol/L
Creatinine	107…182	♂ 64–104 µmol/L · ♀ 49-90 µmol/L
Uric acid	541…593	♂ 210–420 µmol/L · ♀ 150-360 µmol/L
Total Protein	45	64 – 83 g/L
Albumin	23	35 – 52 g/L
AST	45	< 40 U/L
ALT	41	< 41 U/L
LDH	312	135 – 225 U/L
NA	135	136 – 145 mmol/L
K	3.7	3.5 – 5.1 mmol/L
Ca	1.7	2.15 – 2.55 mmol/L
P	1.9	0.8 – 1.5 mmol/L
Triglycerides	3.7	< 1.7 mmol/L
HDL	0.8	♂ >1.0 · ♀ >1.2 mmol/L
C3	0.4	0.9 – 1.8 g/L
C4	0.1	

creased internal dimensions of the left-sided cardiac chambers and globally reduced left ventricular wall motion**.** A small circumferential pericardial effusion was present, measuring approximately 8 mm to the posterior wall of the left ventricle**,** 5 mm anterior to the right ventricle**,** and 4 mm anterior to the apex**.** A small bilateral pleural effusion was also present.

Dermatologic examination showed malar erythematous-desquamative plaques. Face with “butterfly rash”. Immunological tests demonstrated ANA positivity, high anti-dsDNA (225.5 IU/mL), positive anti-Sm (123 IU/mL), and p-ANCA +++, with negative antiphospholipid antibodies.

A renal biopsy performed on the day 3, confirmed lupus nephritis (LUPUS NEPHRITIS class IV/V, with small part of class VI).

Histopathology Report: small blood vessels show changes consistent with "onion-skin" lesions. The remaining tubular epithelium shows changes consistent with protein reabsorption. Considering the DIF (full house pattern), the findings are consistent with Lupus Nephritis, Class IV + V (±VI).

The Activity Index was 10 and Chronicity Index 2.5,

How it relates to Classes: **Class I**-Normal light microscopy; *mesangial immune deposits* seen only by IF/EM; **Class II**-Mesangial hypercellularity/deposits visible in light microscopy; **Class III / IV**-Focal (III) or diffuse (IV) proliferative lesions with *subendothelial deposits*; and **Class V**-Membranous pattern with *subepithelial deposits*.

Treatment included a three days course of high-dose intravenous methylprednisolone (500 mg) followed by tapering, after that with a peroral corticosteroid therapy for a prolonged period. The patient received three doses of cyclophosphamide overall, during hospitalization and three doses after that, repeated every 3 weeks for a total 6 doses. Five plasmapheresis sessions were performed with satisfactory outcome [8,9]. There was no need for hemodialysis. The consultation with rheumatologists included a therapy with hydroxychloroquine.

Follow up during the next month showed improvement of the results and stable state. The results are presented on Table 2.

Table 2. Laboratory findings one month after hospitalization

Analyse	Results	References
Erythrocytes	3.7	4.2 – 5.9 ×10¹²/L
Hemoglobin	121	♂ 135–175 · ♀ 120–155 g/L
Hct	0.34	
PLT	368	150 – 400 ×10⁹/L
Urea	8.2	2.5 – 7.8 mmol/L
Creatinine	90	♂ 64–104 µmol/L · ♀ 49-90 µmol/L
Total Protein	72	64 – 83 g/L
Albumin	42	35 – 52 g/L
NA	140	136 – 145 mmol/L
K	5.0	3.5 – 5.1 mmol/L
Ca	2.4	2.15 – 2.55 mmol/L
P	1.9	0.8 – 1.5 mmol/L
C3	1.6	0.8-1.4
C4	0.2	0.2-0.5

Discussion

SLE is a complex autoimmune and idiopathic condition that affects connective tissues. It is characterized by the formation of autoantibodies, the accumulation of immune complexes, inflammation, and, ultimately, irreversible organ damage. Managing SLE patients involves various approaches and lifestyle recommendations, including avoiding direct or reflected sunlight. The diverse clinical manifestations of SLE present a challenge to the clinician. Several mechanisms lead to a loss of self-tolerance and organ dysfunction. Impressive progress has been made over the last several years toward understanding how almost every aspect of the immune system contributes to the expression of systemic autoimmunity. The kidney is involved in more than half of patients with SLE and contributes significantly to its morbidity. The contribution of autoantibodies with a number of reactivities and of immune complexes in the expression of kidney inflammation has been reviewed extensively over the years. Studies of the involved organs, including skin, the kidney and the brain, have revealed local processes that are responsible for tissue damage. Without ignoring the role of the autoimmune response in the organ damage, it is

possible that the local inflammatory processes proceed independently with little or no outside input. Better understanding of these processes should open new approaches to the disease treatment [8,9].

This case illustrates new-onset SLE presenting with lupus nephritis in the post-partum period. Immune rebound following pregnancy has likely contributed to the disease activation [7,10]. The combination of a nephrotic-range proteinuria, hematuria, malar rash, reduced ejection fraction, and positive autoantibodies pointed strongly toward lupus nephritis, that was biopsy confirmed [6]. Early intervention with corticosteroids, cyclophosphamide [8,9], and plasmapheresis resulted in significant improvement.

Conclusion

Early recognition of lupus nephritis in the post-partum period is crucial for the treatment of the lupus nephritis. This patient achieved complete clinical remission following immunosuppressive therapy and continues under nephrology follow-up due to the possible risk of relapse.

Conflict of interest statement. None declared.

Reference

1. Oxford Handbook of Nephrology and Hypertension, 2nd Edition.Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int* 2021; 100(4S): S1-S276.
2. Tsokos GC. Systemic Lupus Erythematosus. *N Engl J Med* 2011; 365(22): 2110-2121.
3. Rovin BH, Parikh SV, Hebert LA. Lupus Nephritis: Clinical Presentation and Management. *BMJ* 2013; 346: f2328.
4. Fanouriakis A, Kostopoulou M, Andersen J, *et al*. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. *Ann Rheum Dis* 2024; 83(1): 15-29.
5. Fanouriakis A, Kostopoulou M, Alunno A, *et al*. 2019 Update of the EULAR Recommendations for the Management of Systemic Lupus Erythematosus. *Ann Rheum Dis* 2019; 78(6): 736-745.
6. Weening JJ, D'Agati VD, Schwartz MM, *et al*. The Classification of Glomerulonephritis in Systemic Lupus Erythematosus Revisited. *J Am Soc Nephrol* 2004; 15(2): 241-250.
7. Sammaritano LR. Pregnancy and Autoimmune Rheumatic Diseases. *Clin Immunol* 2018; 186: 38-41.
8. Illei GG, Takada K, Parkin D, *et al*, Boumpas DT. Renal flares are common in patients with severe proliferative lupus nephritis treated with pulse immunosuppressive therapy: long-term followup of a cohort of 145 patients participating in randomized controlled studies. *Arthritis Rheum* 2002; 46(4): 995-1002.
9. Padmanabhan A, Connelly-Smith L, Aqui N, *et al*. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice-2019 Update. *J Clin Apher* 2019; 34(3): 171-354.
10. Davidson A, Diamond B. Autoimmune Diseases: The Immune Pathogenesis of SLE. *Immunity* 2001; 14(5): 447-456.
11. Fanouriakis A, Kostopoulou M, Alunno A, *et al*. 2019 Update of the EULAR Recommendations for the Management of Systemic Lupus Erythematosus. *Ann Rheum Dis* 2019; 78(6): 736-745.

BANTAO Journal 2025; 23(2): 46-48

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Case report

Peritoneal Dialysis-Associated Peritonitis Caused by Rare Pathogens: *Cellulosimicrobium Cellulans* and *Brevundimonas Vesicularis*

Gulsum Ceren Terzioglu Yazici, Alper Alp and Bulent Huddam

Department of Nephrology, Faculty of Medicine, Mugla Sıtkı Koçman University, Mugla, Turkey

Abstract

Peritonitis is one of the most important complications of peritoneal dialysis (PD) and a leading cause of PD failure. Most frequently, there are isolated gram-positive microorganisms, and a minor proportion of gram-negative bacteria that is lately increasing. Herein, we present two rare cases of PD-associated peritonitis caused by uncommon microorganisms: *Cellulosimicrobium cellulans* and *Brevundimonas vesicularis.*
We concluded that an early diagnosis and appropriate antibiotic therapy may lead to successful outcomes, even without catheter removal.

Keywords: peritoneal dialysis, gram-negative microorganisms, early diagnosis, antibiotic treatment

Introduction

Peritonitis is one of the most important complications of peritoneal dialysis (PD) and a leading cause of PD failure [1]. Gram-positive microorganisms are most commonly isolated, whereas Gram-negative bacteria account for approximately 15%-35% of all cases [2-4]. However, in recent years, a decrease in the incidence of Gram-positive peritonitis and a corresponding increase in cases caused by Gram-negative organisms have been observed. Herein, we present two rare cases of PD-associated peritonitis caused by uncommon microorganisms: *Cellulosimicrobium cellulans* and *Brevundimonas vesicularis.*

Case 1.

A 49-year-old man presented to the emergency department with a two-day history of abdominal pain and turbid peritoneal fluid. He has been receiving peritoneal dialysis for 4 years. His medical history was notable for diabetes mellitus. At presentation, his vital signs were as follows: blood pressure 112/80 mmhg, pulse rate 100 beats/min, temperature 36 ˚C. Physical examination revealed no additional abnormalities except for abdominal tenderness. The catheter exit site was clean and there was no findings suggestive of tunnel infection. Laboratory tests at admission showed a haemoglobin level of 14.5 g/dl, leukocyte count of 7.26 x 10^3/µL, neutrophil count of 5.23 x 10^3/µL, platelet count of 126.000 x 10^3/µL. Blood urea was 85.4 mg/dl, creatinine was 8.16 mg/dl and C-reactive protein (CRP) level was 120 mg/dl. Analysis of the peritoneal fluid revealed a white blood cell count of 206/µL from which 61.7% were polymorphonuclear leukocytes. Empirical treatment with intraperitoneal ceftazidime 4 g/day and cefazolin 4 g/day was initiated. *Cellulosimicrobium cellulans* growth was detected in peritoneal fluid culture 48 hours after initation of therapy. According to the antibiogram results (Table 1), cefazolin and ceftazidime were discontinued and intravenous vancomycin 1000 mg was initiated. As no dialysis failure occured during the course of peritonitis, haemodialysis was not required. On the fifth day of treatment, the dialysate leukocyte count decreased to 61/µL. The patient was discharged after completing the three-week course of vancomycin therapy.

Table 1. *Cellulosimicrobium cellulans* antibiotic susceptibility pattern

Antibiotic	Susceptibility
Piperacilin/Tazobactam	Resistance
Ciprofloxacin	Resistance
Imipenem	Resistance
Colistin	Resistance
Cefepime	Resistance
Ceftazidime	Resistance
Levofloxacin	Resistance
Vankomicin	Sensitive

Case 2.

A 46-year-old male patient admitted to the emergency department with a 2-day history of abdominal pain and cloudy peritoneal fluid. He has been receiving peritoneal dialysis for 5 years. His medical history was notable for hypertension and coronary artery disease. At admission, his vital signs were as follows: blood pressure 112/80 mmHg, pulse rate 100 beats/min, fever

Correspondence to: Gulsum Ceren Terzioglu Yazici, Department of Nephrology, Faculty of Medicine, Mugla Sitki Kocman University, Mugla, Turkey; E-mal: dr.gulsumcerenyazici@gmail.com

36˚C. Physical examination revealed abdominal tenderness, with no other abnormal findings. The catheter exit site was clean and there were no signs suggestive of tunnel infection. Laboratory investigations showed haemoglobin level of 15.6 g/dl leukocyte count of 6.13 x 10^3/µL neutrophil count of 4.85 x 10^3/µL platelet count of 113.000 x 10^3/µL. Serum urea and creatinine levels were 92 mg/dl and 6.9 mg/dl, respectively, while CRP level was 111.31 mg/dl. Analysis of the peritoneal fluid revealed a leukocyte count of 3854/µL, of which 86.3% were polymorphonuclear leukocytes. Dialysate culture was examined due to the suspected peritonitis. Empirical treatment with intraperitoneal ceftazidime 4 g/day and cefazolin 4 g/day was initiated. After 48 hours, *Brevundimonas vesicularis* growth was isolated from the peritoneal fluid culture. Based on antibiogram (Table 2), cefazolin and ceftazidime were discontinued and intravenous amikacin 1000 mg was initiated. Since no dialysis failure occured during the episode of peritonitis, haemodialysis was not required. On the fifth day of treatment, the dialysate leukocyte count was 24/ µL. The patient was discharged after completing a 3-week course of amikacin treatment.

Table 2. *Brevundimonas vesicularis* antibiotic susceptibility pattern

Antibiotic	Susceptibility
Piperacilin/Tazobactam	Resistance
Ciprofloxacin	Resistance
Imipenem	Resistance
Colistin	Resistance
Cefepime	Resistance
Ceftazidime	Resistance
Levofloxacin	Resistance
Amikacin	Sensitive

Discussion

Although the exact source of infection could not be determined, environmental exposure and contamination during peritoneal dialysis procedures should be considered. Both *Brevundimonas vesicularis* and *Cellulosimicrobium cellulans* have been isolated from environmental sources, including water and soil, suggesting that accidental inoculation through contaminated dialysis equipment, dialysis fluids, touch contamination during exchanges, or lapses in aseptic technique may represent plausible routes of infection in PD patients.

Among gram negative bacteria, *Brevundimonas spp.* are rarely implicated in human infections according to the available literature [5]. In a review conducted by Shang *et al*., in 2012, only 15 cases of bacteraemia caused by these bacteria were reported [6]. Peritonitis due to *Brevundimonas vesicularis* is extremely rare, and therefore, data regarding its antibiotic susceptibility are limited.

Additionally, although 31 cases of infection caused by *Cellulosimicrobium cellulans* have been reported in the literature, only four of these were associated with peritonitis [**7**]. In most previously reported cases, catheter removal was required for a successful treatment. According to the 2022 ISPD guidelines, catheter removal is recommended in refractory or treatment-resistant peritonitis [8]. In contrast, in our case, peritonitis was successfully treated with intraperitoneal vancomycin without the need for catheter removal.

Christiadi *et al*., successfully treated a case of peritonitis caused by *Brevundimonas vesicularis*-associated peritonitis using a 21-day regimen consisting of intraperitoneal gentamicin (10 days), cefepime (11 days) and oral ciprofloxacin (11 days), based on treatment protocol recommended for *Pseudomonas aeruginosa* [9]. In contrast, in the case reported by Paramasivam *et al*., the peritoneal catheter had to be removed due to treatment resistance [5]. In our patient, antibiotic susceptibility testing revealed sensivity to amikacin and the patient responded well to daily intravenous amikacin therapy.

Conclusion

In conclusion, *Brevundimonas vesicularis* and *Cellulosimicrobium cellulans* have been reported as rare causes of peritoneal dialysis-associated peritonitis. Early diagnosis and appropriate antibiotic therapy may lead to successful outcomes, even without catheter removal. These cases highlight that individualized antibiotic selection based on susceptibility testing can be effective in selected patients. Furthermore, our cases contribute to the limited literature on these uncommon pathogens by demonstrating that conservative management with targeted antimicrobial therapy may be a feasible alternative to the catheter removal in carefully selected patients who respond to treatment. Thus, these organisms should be considered in the differential diagnosis of peritonitis in patients undergoing peritoneal dialysis.

Conflict of interest statement. None declared.

References

1. Gadola L, Poggi C, Dominguez P, *et al*. Risk factors and prevention of peritoneal dialysis-related peritonitis. *Perit Dial Int* 2019; 39(2): 119-125.
2. Kim DK, Yoo TH, Ryu DR, *et al*. Changes in causative organisms and their antimicrobial susceptibilities in CAPD peritonitis: a single center's experience over one decade. *Perit Dial Int* 2004; 24: 424.
3. Mujais S. Microbiology and outcomes of peritonitis in North America. *Kidney Int Suppl* 2006; S55.
4. Oo TN, Roberts TL, Collins AJ. A comparison of peritonitis rates from the United States Renal Data System database: CAPD versus continuous cycling peritoneal dialysis patients. *Am J Kidney Dis* 2005; 45: 372.

5. Paramasivam V, Paez A, Verma A, *et al*. Brevundimonas Vesicularis peritonitis in a chronic peritoneal dialysis patient. *Nephrol Dial* 2021; 11(3): 314-320.
6. Shang ST, Chiu SK, Chan MC, *et al*. Invasive *Brevundimonas vesicularis* bacteremia: two case reports and review of the literature. *J Microbiol Immunol Infect* 2012; 45(6): 468-472.
7. Kim J S, Tae W L, Ihm CG, *et al*. CAPD peritonitis caused by co-infection with Cellulomicrobium Cellulans (Oerskovia Xanthineolytica) and Enterobacter Cloacae: A Case Report and Literature Review. *Intern Med* 2015; 54: 627-630.
8. Li PKT, Szeto CC, Piraino B, *et al*. ISPD peritonitis recommendations: 2022 update on prevention and treatment. *Peritoneal Dialysis International* 2022; 42(2): 110-153.
9. Christiad D, Singer RF, Roberts DM. Successful treatment of PD peritonitis due to Brevundimonas Vesicularis. *Perit Dial Int* 2018; 38(5): 379-381.

BANTAO Journal 2025; 23(2): 49-50

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Letter to the editor

When to suspect Ig A nephropathy and Timing of Kidney Biopsy

Kubra Kaynar

Department of Nephrology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey

Dear Editor,

Immunoglobulin A nephropathy (IgAN) is the most common cause of primary glomerulonephritis worldwide [1]. It was first defined in 1968 by (two kidney pathologists) Jean Berger and Nicole Hinglais, in kidney biopsies with chronic mesangial proliferative glomerulonephritis associated with dominant or codominant IgA deposits observed by immunofluorescence [2]. Few cases (nearly 10%) are due to familial IgAN whereas more than 90% of IgAN cases are sporadic [3].
The four hit model was defined for pathogenesis. The first hit is the production of galactose-deficient (Gd) IgA1 by gut including the Peyer patches, and nasal mucosa, second hit is the production of autoantibodies (IgG, IgA, or IgM) against these Gd-IgA1 which were secreted into blood vessels, the third hit is the formation of immune complexes, and the fourth hit is the binding of these immune complexes to the kidney mesangial cells leading to activation of proliferative, fibrotic, and inflammatory pathways [4,5].
The prevalence of IgAN differs between the countries (11.8% in North America, 39.5% in Asia, 22.1% in Europe, and 6.1% in Latin America) [6]. These variations in prevalence of IgAN may reflect geographical differences in screening for kidney disease and kidney biopsy practices because the definitive diagnosis of IgAN can only be made by evaluation of a kidney biopsy [6]. This difference in prevalence may also be associated with genetic factors and environmental influences in addition to presence or absence of urinary screening programs and indications for kidney biopsy.
The clinical presentation of IgAN also varies between the patients with a range of signs and symptoms from asymptomatic urine abnormality, macroscopic hematuria (20-25%), to nephrotic syndrome and chronic renal impairement [7]. In Japan, China, and Korea, it is mandatory to screen school students for early morning urinary hematuria [8]. Proteinuria accompanied by hematuria warrants a complete medical workup and kidney biopsy. So, exact prevalence is uncertain due to these differences in clinical presentations, screening programs for kidney diseases, and kidney biopsy indications to confirm the diagnosis.

The clinical presentations of IgAN range from asymptomatic hematuria to rapidly progressive glomerulonephritis. Brown, red, or cola colored urine, hypertension, acute kidney injury, frothy urine, synpharyngitic hematuria, hypervolemia (edema, basal lung crepitations), and recurrent episodes of macroscopic hematuria can be found in medical history and physical examination of patients with IgAN [3]. The diagnosis of IgAN should be suspected in any patient with one or more episodes of macroscopic hematuria, especially if accompanied by an upper respiratory or gastrointestinal infection, persistent microscopic hematuria (present in 93% of the patients) with or without proteinuria not otherwise explained, and slowly progressive kidney function impairment without any other reason [9].
Based on a study, patients with three or four markers (more than five red blood cells in urinary sediments; persistent proteinuria of more than 0.3 g/day; serum IgA levels of more than 315 mg/dL and serum IgA/C3 ratio of more than 3.01) have the 75% risk of IgA nephropathy [10]. Although an elevated IgA/C3 ratio is still biologically plausible, and can help initial triage, sensitivity and sprecificity are insufficient for clinical decision making. KDIGO 2021 does not endorse IgA/C3 ratio as a diagnostic criterion.
Although patients with three or four markers (more than five red blood cells in urinary sediments; persistent proteinuria of more than 0.3 g/day; serum IgA levels of more than 315 mg/dL and serum IgA/C3 ratio of more than 3.01) were reported to have the 75% risk of IgAN, IgAN can be diagnosed only by kidney biopsy by showing mesangioproliferative glomerulonephritis with dominant or codominant depositions of IgA [9,10]. Because there are no validated serum or urine biomarkers for the diagnosis of IgAN yet.In order to ensure early and prompt diagnosis and treatment of IgAN, kidney biopsy is indicated for all adults with proteinuria ≥0.5g/d and a possible diagnosis of IgAN without any contraindication of kidney biopsy [11]. Before biopsy, serum complement levels (C3, C4, CH50), viral serologies (human immunodeficiency virus, hepatitis B, and C), autoantibodies (antinuclear, anti-double stranded DNA, antineutrophil cytoplasmic, extractable nuclear antigen, and antiphospholipid antibodies), glycated hemoglobin (HbA1c), protein elec-

Correspondence to: Kubra Kaynar, Karadeniz Teknik Universitesi, Tıp Fakultesi, Nefroloji Bilim Dalıı, 61080 Trabzon, Turkey; E-mail: kkaynar@yahoo.com

trophoresis (older than 50 years), anti-PLA2R autoantibody should be evaluated if possible [12].

Timing of kidney biopsy for the early and prompt diagnosis of IgAN is very important. Because by the time IgAN diagnosis, unfortunately more than 50% (74.6%) of adult patients already have chronic kidney disease (CKD) stage 3 or greater [13]. The delay in diagnosis exposes kidneys to persistent injury resulting in progression to irreversible kidney failure [13]. The prognosis among patients with IgAN also is not similar, just like the differences in prevalence and clinical presentations of IgAN [14]. Outcomes in IgAN cohorts are generally worst in poor prognosis group with possibility of dialysis in 5 years [14]. The prognostic parameters are listed as age, race, proteinuria, systolic and diastolic blood pressure, medication used, estimated GFR, and histologic score (MEST) of kidney biopsy [15]. Urinary albumin creatinine ratio of more than 0.1 g/g was reported to be independently associated with greater risk of composite kidney events in patients with IgAN [16]. As more studies and data are received regarding the timing for kidney biopsy to achieve prompt diagnosis of IgAN, the indications for kidney biopsy may change accordingly. Until then, KDIGO 2025 clinical practice guideline should be followed for biopsy timing of patients with IgAN.

Once IgA nephropathy is confirmed by kidney biopsy, secondary causes-including systemic diseases, chronic infections, malignancies, and drug exposure-should be actively investigated to allow early diagnosis and appropriate treatment. Crohn's disease, ulcerative colitis, celiac disease, HIV infection, psoriasis, cirrhosis, Lyme disease, malaria, osteomyelitis, cat scratch disease, renal cell carcinoma, and use of dabigatran, warfarin, ustekinumab, should be searched in order to diagnose and treat early and appropriately [17].

In conclusion, it should be known that by the diagnosis of IgAN, unfortunately most of the patients already have severe and irreversible kidney injury. In order not to be late for prompt treatment of these patients, clinicians should be aware of the clues for the presence of IgAN in medical history, physical examination, urine and blood tests of the patients so that optimal timing of kidney biopsy is not missed.

Conflict of interest statement. None declared.

References

1. Pawluczyk I, Nicholson M, Barbour S, *et al*. A Pilot Study to Predict Risk of IgA Nephropathy Progression Based on miR-204 Expression. *Kidney Int Rep* 2021; 6(8): 2179-2188.
2. Berger J, Hinglais N. Les ddpôts intercapillaires d'IgA-IgG [Intercapillary deposits of IgA-IgG]. *J Urol Nephrol (Paris)* 1968; 74(9): 694-695.
3. Rout P, Afzal M. IgA Nephropathy (Berger Disease). 2024 Apr 22. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.
4. El Karoui K, Fervenza FC, De Vriese AS. Treatment of IgA Nephropathy: A Rapidly Evolving Field. *J Am Soc Nephrol* 2024; 35(1): 103-116.
5. Ramsawak S, Cohen S, Linares A, Cavanaugh C. IgA nephropathy: Update on pathogenesis and treatment. *Cleve Clin J Med* 2025; 92(6): 373-383.
6. O'Shaughnessy MM, Hogan SL, Thompson BD, *et al*. Glomerular disease frequencies by race, sex and region: results from the International Kidney Biopsy Survey. *Nephrol Dial Transplant* 2018; 33(4): 661-669.
7. Lai KN, Tang SC, Schena FP, *et al*. IgA nephropathy. *Nat Rev Dis Primers* 2016; 2: 16001.
8. Honda K, Akune Y, Goto R. Cost-Effectiveness of School Urinary Screening for Early Detection of IgA Nephropathy in Japan. *JAMA Netw Open* 2024; 7(2): e2356412.
9. Cheung CK, Barrat J. IgA nephropathy: Clinical features and diagnosis. 2025 Nov. UpToDate.com. Available at https://www.uptodate.com/contents/iga-nephropathy-clinical-features-and-diagnosis date accessed: 10/12/2025.
10. Nakayama K, Ohsawa I, Maeda-Ohtani A, *et al*. Prediction of diagnosis of immunoglobulin A nephropathy prior to renal biopsy and correlation with urinary sediment findings and prognostic grading. *J Clin Lab Anal* 2008; 22(2): 114-118.
11. Kidney Disease: Improving Global Outcomes (KDIGO) IgAN and IgAV Work Group; Rovin BH, Barratt J, Cook HT, Noronha IL, Reich HN, Suzuki Y, Tang SCW, Trimarch H, Floege J. KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV). *Kidney Int* 2025; 108(4S): S1-S71.
12. Radhakrishnan J. Glomerular disease: Evaluation and differential diagnosis in adults. 2025 Nov. UpToDate.com. Available at https://www.uptodate.com/contents/glomerular-disease-evaluation-and-differential-diagnosis-in-adults? date accessed: 10/12/2025.
13. Caster DJ, Abner CW, Walker PD, *et al*. Clinicopathological Characteristics of Adult IgA Nephropathy in the United States. *Kidney Int Rep* 2023; 8(9): 1792-1800.
14. Tomino Y. Immunoglobulin A nephropathy and chronic kidney disease. *Nephrology (Carlton)* 2010; 15(Suppl 2): 23-26.
15. Barbour SJ, Coppo R, Zhang H, *et al*. Evaluating a New International Risk-Prediction Tool in IgA Nephropathy. *JAMA Intern Med* 2019; 179(7): 942-952.
16. Stamellou E, Nadal J, Hendry B, *et al*. GCKD study investigators. Long-term outcomes of patients with IgA nephropathy in the German CKD cohort. *Clin Kidney J* 2024; 17(8): sfae230.
17. Tota M, Baron V, Musial K, *et al*. Secondary IgA Nephropathy and IgA-Associated Nephropathy: A Systematic Review of Case Reports. *J Clin Med* 2023; 12(7): 2726.

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