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LITERATURE REVIEW

# INTENSIVE NEPHROLOGY FROM THE PERSPECTIVE OF TRANSLATIONAL RESEARCH: NARRATIVE REVIEW AT THE FRONTIER OF KNOWLEDGE

## NEFROLOGIA INTENSIVA SOB A PERSPECTIVA DA PESQUISA TRANSLACIONAL: REVISÃO NARRATIVA NA FRONTEIRA DO CONHECIMENTO

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**Abstract**
**Introduction:** Intensive nephrology contemplates renal pathologies that affect critically ill patients under intensive care and, as it is an recent area of knowledge, it still demands studies that explore alternatives for diagnosis and treatment, in addition to a better pathophysiological understanding of kidney injuries in this level of care, highlighting opportunities for the application of translational research. **Objective:** This review aims to delimit the current state of the art and understand where are the frontiers of knowledge in intensive nephrology, in its diagnostic, therapeutic aspects and future perspectives. **Methodology:** This study is a narrative review that carried out extensive research in the literature, including reference papers and databases (PubMed Medline, Google Academics, Scielo and LILACS), selecting articles with potential application in the community and compiling the results in a structured way. They were used as descriptors in the bases: nephrology, biomarkers, translational research and acute kidney injury and the delimited languages were english and portuguese with a focus on the thresholds of diagnosis, treatment and the expectations of using these fundamentals. **Results:** Update on biomarkers in evidence, such as Kim-1, in addition to contemporary treatment options for intervention in cell metabolism, protein modulation, prescription of antioxidants or anti-apoptotics, use of new drugs and even current ones discussions of renal replacement therapy in the intensive care setting. **Conclusion:** This narrative review enabled an understanding of the present moment in intensive nephrology, the use of new biomarkers and the frontiers that need to expand translational research for the benefit of patients.

**Keywords:** Nephrology; Biomarkers; Translational Research.

**Resumo**
**Introdução:** A nefrologia intensiva contempla patologias renais que acometem pacientes críticos sob cuidados intensivos e por ser uma área recente do conhecimento, ainda carece de estudos que explorem alternativas de diagnóstico e tratamento, além do melhor entendimento fisiopatológico das lesões renais nesse nível de cuidado, evidenciando oportunidades para a aplicação da pesquisa translacional. **Objetivo**: A presente revisão visa delimitar o atual estado da arte e entender onde estão as fronteiras do conhecimento na nefrologia intensiva, em seus aspectos diagnóstico, terapêutico e de perspectivas futuras. **Métodos**: Este estudo trata-se de uma revisão narrativa que realizou ampla pesquisa na literatura, incluindo obras de referência no tema e bases de dados (PubMed

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Medline, Google Academics, Scielo e LILACS) selecionando artigos com potencial aplicação na comunidade e compilou os resultados de modo estruturado. Utilizados como descritores nas bases: nefrologia, biomarcadores, pesquisa translacional e injúria renal aguda e os idiomas delimitados foram o inglês e o português com enfoque sobre os limiares do diagnóstico, tratamento e as expectativas de emprego desses fundamentos. **Resultados:** Atualização sobre os biomarcadores em evidência nas pesquisas, como o Kim-1, além das opções contemporâneas de tratamento por intervenção no metabolismo celular, na modulação de proteínas, na prescrição de antioxidantes ou antiapoptóticos, na utilização de novos fármacos e ainda as atuais discussões da terapia substitutiva renal no ambiente de cuidado intensivo. **Conclusão:** Esta revisão narrativa possibilitou um entendimento do presente momento da nefrologia intensiva, uso de novos biomarcadores e as fronteiras que necessitam ampliar as pesquisas translacionais para o benefício dos pacientes.

**Palavras-chave:** Nefrologia; Biomarcadores Farmacológicos; Pesquisa Translacional Biomédica.

## INTRODUCTION

Translational research is characterized as a multidisciplinary area of medical investigation and results from the challenge of transferring to the community the knowledge acquired in the basic research, combined with clinical applications at the patient´s bedside. The European Society for Translational Medicine emphasizes the “community” pillar as a key partner and major beneficiary of all translational interventions [1].

Intensive care nephrology is identified as an area of nephrology that involves issues in interface with intensive care medicine [2]. It is a science of recent emergence, corroborated by the greater use of this nomenclature only at the end of the 1990s, the topic of intensive nephrology itself is on the frontiers of knowledge between nephrology and intensive care medicine. Therefore, intensive nephrology emphasizes its contemporaneity and the pertinence of its themes for the development of translational research.

Acute kidney injuries in critically ill patients make up the largest spectrum of action in intensive nephrology, however, this area also studies renal replacement therapy (RRT) in intensive care units (ICU), renovascular arterial hypertension in critically ill patients, hydroelectrolytes and acid-bases of acute onset and nephroprotection measures in the ICU environment. Intensive nephrology also participates in discussions about the limitation of clinical support and the patient's terminality.

Translational research has the potential to promote the individualization of the approach in intensive nephrology, as the discovery of a new marker could help in the decision to start RRT or the finding of a new cellular receptor would motivate the development of substances for the treatment of kidney dysfunction. Thus, it is possible to customize the clinical care of the renal patient with the knowledge obtained from the experimental phase of the research.

However, where are we in the state of the art of intensive nephrology? Which areas of research have not yet shown evidence of a translation of knowledge to a focus on the community? Later, these analyzes will be presented for the construction of an understanding.

This review aims to delimit the current state of the art and understand the frontiers of knowledge in intensive nephrology with its diagnostic or therapeutic aspects and future perspectives.

## METHODOLOGY

The research for this narrative review brought together the knowledge of reference works on the subject of intensive nephrology and translational research, in addition to the search in the databases (PubMed Medline, Google Academics, Scielo and LILACS) using the descriptor terms nephrology, biomarkers, translational research and acute kidney injury. The languages delimited were English and Portuguese with preference for publications from the last 05 years, however, without temporal limitation.

The resulting information was collected and compiled in the themes state of the art, frontiers of diagnosis, frontiers of treatment and future perspectives for the application of knowledge, in order to facilitate the understanding and presentation.

## STATE OF THE ART IN INTENSIVE NEPHROLOGY

- Acute Kidney Injury

Acute kidney injury (AKI) is the main clinical condition of interest to Intensive Nephrology, whose terminology refers to damage and injury, but not only to the advanced stage of failure. Therefore, what defines this condition is the reduction of function and not the associated structural deterioration.

The risk factors that trigger the syndrome and its prevention measures are well established and known in the literature. The stages of AKI based on serum creatinine levels and urine output constitute the classification of KDIGO [3] (Kidney Disease: Improving Global Outcomes).

In the therapeutic scope, the volemic resuscitation protocol, in cases of shock or hypoperfusion, as well as the use of vasopressors and inotropes seeking adequate levels of pressure and perfusion are consolidated strategies in patient´s bedside practice. It is noteworthy that treatment with fenoldopam, atrial natriuretic peptide, insulin-like growth factor and “renal” doses of dopamine has proven ineffectiveness in intensive nephrology [4].

- Sepsis and Microcirculation: Origins of AKI?

Different pathophysiological mechanisms are involved in hypoperfusion and dysfunction of multiple organs and systems caused by sepsis, however, the main focus is on microcirculation, related to thrombus formation, endothelial disfunction and interstitial edema [2]. In this context, the neurohumoral action of nitric oxide is fundamental, which contributes to systemic vasodilation in sepsis and results in pathological vascular shunts [5].

On the other hand, there is an activation of the renin-angiotensin-aldosterone system seeking a compensatory vasoconstriction in sepsis. This action, even without a powerful systemic effect, induces renal vasoconstriction and progresses to acute renal failure. The present sequence of events demonstrates the participation of nitric oxide in AKI processes.

## FRONTIERS OF DIAGNOSIS

Borderline conditions are a research challenge regarding classification and diagnosis in intensive nephrology. For example, the clinical events of progressive loss of renal function in a more accelerated way are mentioned, however, in a period of more than 03 months, which would not characterize a recurrent course and would be beyond the scope of AKI. These conditions would be described as subacute situations in the current context. Furthermore, the low sensitivity and specificity of classic kidney injury markers encourage research into new alternatives for the diagnostic tools.

- Biomarkers

The challenge of identifying subclinical acute kidney injury, before the onset of renal failure, is one of the motivations for studying biomarkers. These biomarkers have good prognostic value in intensive nephrology, however, they lack the translational application of their findings.

The main biomarkers that motivate research are listed below and the gaps in the respective studies that limit the dissemination of its clinical use in the community are mentioned:

1. KIM-1 (Kidney injury molecule 1):

This glycoprotein has been the subject of studies regarding its elevation in cases of renal ischemia or nephrotoxicity, however, there are still few studies about the applicability of KIM-1 in septic patients. Likewise, the usefulness of its serum measurement also needs validation, as most studies use the urinary level as a parameter, mainly in animal models. Promising interpretations have emerged regarding the possibility of using KIM-1 as an inflammation marker in sepsis, before the onset of AKI, measured both in serum and urine samples. However, its usefulness in predicting severity is still limited [6] and these gaps are opportunities for translational research.

2. NGAL (Neutrophil gelatinase-associated lipocalin):

The NGAL has a gap in research due to the diversity of the populations studied, a fact that did not allow establishing who would benefit from its use. Furthermore, the best way for its measurement (plasma or urinary) also lacks consensus in the literature.

3. IL-18 (Interleukin 18):

Presented as a pro-inflammatory cytokine, IL-18 plays an active role in inflammatory activity and appears to participate in AKI processes, also observed in experimental research. The benefit of its measurement in sepsis states is still undefined, since some studies relate it to the severity and prognosis of sepsis-related AKI, but its predictive or diagnostic function is still uncertain and lacks validation [7].

4. Cystatin C:

Cystatin C is an inhibitor of tissue cystine protease and the subject of research regarding its ability to measure kidney function more accurately compared to creatinine. The frontiers of research on this protein lie in establishing parameters and validation for its use in cases of AKI due to sepsis, in defining the ideal means for measurements (serum or urine?) and in its prediction for recovering the renal function [8].

5. L-FABP (Liver fatty-acid binding proteins):

The L-FABP are cytoplasmic proteins expressed in cells that metabolize fatty acids and have been studied as an early marker of AKI. In an animal model, L-FABP appear to reflect the degree of renal hypoxia and the progression to chronic kidney disease [9], but these data need to be translated into the practice of intensive nephrology.

6. NAG (N-acetyl-D-glucosaminidase):

A member of the urinary tubular enzymes, NAG is highly sensitive for the perception of AKI in critically ill patients, preceding creatinine elevation by 12-14 days [10]. There are gaps in research about what would be the reference values for the differential diagnosis between pre-renal and renal AKI.

7. FGF23 (Fibroblast growth factor 23):

Despite the knowledge that FGF23 increases gradually as AKI progresses to insufficiency [11], it is still unclear whether FGF23 is only a marker of disease severity or if it also contributes to adverse effects in severe ill patients. Thus, translational clinical studies are needed in the practice of intensive nephrology.

Biomarker options for intensive nephrology also include retinol biding protein (RBP), alpha-glutathione S-transferase (alpha-GST), pi-glutathione S-transferase (pi-GST) and alanine aminopeptidase (AAP), with different stages of research and application between them. Table 1 includes the renal biomarkers used in intensive nephrology and their respective classes.

**Table 1**: Biomarkers in Intensive Nephrology.

| BIOMARKERS CLASSES | DESCRIPTION |
|---|---|
| Up-regulated proteins | NGAL[1], KIM-1[2], IL-18[3], FGF23[4] and L-FABP[5] |
| Low molecular weight proteins | Cistatyn C urinary and RBP[6] |
| Enzymes | NAG[7], alpha-GST[8], pi-GST[9] and AAP[10] |

[1]Neutrophil gelatinase-associated lipocalin, [2]Kidney injury molecule, [3]Interleukin 18, [4]Fibroblast growth factor 23, [5]Liver-type fatty acid-binding protein, [6]Retinol binding protein, [7]N-acetil-B-D-glucosaminidase, [8]Alpha-glutathione s-transferase, [9]Pi-glutathione S-transferase and [10]Alanine aminopeptidase. **Origin:** The author.

Another frontier in diagnostic support with renal biomarkers is the measurement of cell stress, even before cell damage occurs. If it were possible mesure cell cycle arrest as a defense mechanism against acute aggression, it could help in establishing an early therapy, suppressing the cascade of deleterious effects to the kidney. Along this way, we have the combination of tissue inhibitor of metalloproteinases-2 (TIMP-2) with insulin-like growth factor binding protein 7 (IGFBP7) [12] that still require further research to analyze its accuracy and diagnostic application in the community.

After all this arsenal presented, it is worth mentioning that one of the strategies studied for the application of biomarkers is to use a panel of biomarkers throughout the evolution of AKI and not just a single marker. The objective is to identify the evolutionary phase, the therapeutic possibility and the prognosis of this condition. This panel is also a challenge for clinical practice.

Limiting questions for the wide use of these biomarkers in intensive nephrology still need to be answered and characterize possibilities for the translational use of knowledge: What is the best biomarker when the date of the insult that led to the AKI is unknown? In the association of comorbidities (sepsis, chronic kidney disease...) what is the best AKI biomarker? What is the specificity of the biomarker regarding the etiology of kidney injury? What kind of biomarker would help in risk stratification to predict severity? Is the biomarker easy to measure and affordable for wide use?

These answers and evidence are objectives that instigate and motivate translational research.

## FRONTIERS OF TREATMENT

The treatment gaps in Intensive Nephrology become evident when we establish an idea: Even if a biomarker is able to identify AKI early, there would not be a specific therapy for the treatment of a kidney disfunction of septic or toxic etiology. This premise motivates us to look at basic research for possibilities of clinical use of new treatments.

- Cellular Metabolism

The conception that the cell needs energy for growth, multiplication and for its functions is something consolidated, as well as the molecular and biochemical processes to generate energy are known. However, the notion of modifying the cellular metabolic activity through the modulation of its transcriptional programs and the regulation of its energetic activities is recent, being one of the current focuses of studies on the cellular therapy [13].

Currently, the most studied proteins as metabolic sensors of inflammatory activity and with potential for therapeutic intervention in Intensive Nephrology are listed below:

1.mTOR (mammalian target of rapamycin):

It is present in mTORC1 and mTORC2 complexes, with mTORC1 being related to compensatory renal hypertrophy and activation of fibroblasts that contribute to inflammation and interstitial fibrosis [14]. However, the studies are limited to the evaluation in podocytes, still requiring studies in other renal cell types. So far, there is no research on its potential participation in the progression to chronicity in AKI.

2.AMPK (protein kinase AMP-activated):

AMPK participates in the regulation of tubular ionic transporters, in addition is involved in mechanisms of renal ischemia, hypertrophy and inflammation. Stimulation of AMPK activity increased water and sodium reabsorption by the kidney *in vitro* and in animal models [15], but *in vivo* data still need to be obtained to understand its physiology and possible use in treatment of nephrogenic edematous syndrome.

3.PPAR (peroxisome proliferator-activated receptor):

They constitute transcription factors and metabolic sensors of fatty acids that regulate lipid metabolism and participate in immune responses as anti-inflammatory mediators. Experimental models of sepsis and acute renal failure showed that a lower expression of PPAR is related to worse renal function and increased interstitial fibrosis [16], however, clinical studies for the practical application of this knowledge in humans are needed.

- Protein Modulation

1.SIK-1 (salt inducible kinase 1):

It is part of the AMP-activated protein kinases family and its suppression induces inflammation and fibrosis, increasing the risk of progression to chronification from AKI observed in animal models [17]. An approach to its stimulation or replacement would be an alternative to delay or prevent the progression to chronic kidney disease in an initial situation of AKI and takes place at the frontier of treatment in intensive nephrology.

2.Exendin-4:

Glucagon-like peptide-1 analogue, whose replacement or stimulation reduces inflammatory activity, apoptosis and oxidative stress in animal models of AKI [18]. Treatment with Exendin-4 would protect the kidney from an ischemia-reperfusion injury progressing to renal failure, although this statement lacks translational proof.

- Antioxidant and anti-apoptotic agentes

The events that trigger AKI lead to the emergence of free radicals and the activation of oxidative stress pathways that initiate mechanisms of inflammatory activity and result in pro-apoptotic events, cell death and worsening of the kidney injury to stages of renal failure.

Intervening in this events pathways with the use of antioxidant and anti-apoptotic agents is one of the frontier limits of therapeutic knowledge in intensive nephrology and some options are listed below:

1.Caspase inhibition:

The inhibition or blocking of caspase pathways would promote an anti-apoptotic effect and a better outcome of kidney injury, however, research in this area is still limited to experimental studies that have shown recovery of kidney function and cell anti-apoptosis effect with the use of Ligustrazine as an agent caspase inhibitor [19], without the translation of this knowledge.

2.L-carnitine:

Antioxidante que atua evitando o acúmulo de produtos da peroxidação lipídica. Em modelos animais, demonstrou eficácia em reduzir a lesão renal por nefrotoxicidade da gentamicina e por LRA mioglobinúrica [20]. Porém, ainda sem evolução dessas pesquisas para a aplicação clínica ou na comunidade.

Antioxidant agent that works by preventing the accumulation of lipid peroxidation products. In animal models, it has demonstrated efficacy in reducing renal injury due to gentamicin nephrotoxicity and myoglobinuric AKI [20]. However, there is no evolution of these researches for clinical application.

3.Klotho:

The Klotho gene encodes a protein expressed mainly in the distal renal tubules that is reduced in ischemia-reperfusion AKI. This protein has a dual function, it acts as an early AKI biomarker and as a possible nephroprotective factor, since its administration would reverse the acute kidney damage caused by this mechanism in experimental studies [21], requiring translation to evaluate this applicability.

4.Other antioxidants agents:

Studies with antioxidant agents such as vitamins C and E, uric acid, N-acetylcysteine and statins showed limited results in experimental models and with possible application in specific situations such as AKI due to nephrotoxicity.

- Drugs and new therapies in Intensive Nephrology

1.Sitagliptin:

Sitagliptin acts on the suppression of inflammatory activity and reduction of apoptosis and oxidative stress, preventing the kidney from the acute worsening of renal injury in experimental models [18]. However, further research is still needed to apply this knowledge in clinical practice and in the scientific community.

2.Dexmedetomidine:

It inhibits the action of the Janus Kinase and the Signal Transducer and Activator of Transcription (JAK/STAT), reduces the inflammatory activity and the kidney damage caused by ischemia-reperfusion injuries in animal models [22]. It is necessary to clinically evaluate this knowledge from experimental research.

3.MG53 (mitsugumin-53):

This protein is primarily expressed in muscle cells and helps protect these cells from injury. However, MG53 is also expressed in proximal tubular cells of the kidney and mediates cell membrane repair. In experimental models of ischemia-reperfusion renal injury, intravenous infusion of this protein protected the kidney from additional damage and stimulated cell repair, showing potential for a preventive and therapeutic approach to AKI with good possibilities of translation into clinical practice [23].

- Renal Replacement Therapy

The progression of AKI results in reduced hydroelectrolytic homeostasis and the deleterious effects of uremia. In this scenario, RRT is the therapeutic alternative for the clinical balance.

Current research on RRT in intensive nephrology focuses on identifying the best time to begin therapy (early or late) and which parameters should be used to decide for its suspension; whether clinical, laboratory criteria, recovery markers or a panel containing a set of these elements.

Finally, another challenge for the therapeutic opportunities of AKI would be to answer the question: “Would blocking the action of nitric oxide improve the outcome of AKI through the effect on microcirculation?” and in this context, new lines of research would emerge.

## FINAL CONSIDERATIONS AND FUTURE PERSPECTIVES

This review intended to present intensive nephrology and its translational application, stimulating scientific curiosity after the advent of the COVID-19 pandemic, which motivated all health staff to look back to the basic research in search of answers for treatment of your patients.

The translational options are wide and range from the understanding and verification of pathophysiological mechanisms, crossing diagnosis and treatment, concluding with prognostic factors and clinical recovery.

Comprehensive questions such as: who? at what time? which markers? what treatments? share attention with more specific questions such as whether the possibility of early blockade of mTOR in AKI would reduce the progression to chronicity.

The translational look directed at intensive nephrology sees a favorable and instigating scenario for the researcher to convey to the community the knowledge produced in basic research.

## REFERENCES

1. Cohrs RJ, Martin T, Ghahramani P, Bidaut L, Higgins PJ, Shahzad A. Translational Medicine definition by the European Society for Translational Medicine. New Horizons Transl Med [Internet] 2015;2(3):86–8. Disponível em: https://www.sciencedirect.com/science/article/pii/S2307502314000782.

2. Yu L, Marques IDB, Costa MC, Burdmann EA. Nefrologia Intensiva. Rio de Janeiro: Roca; 2016. 392p.

3. Kidney Disease improving global outcomes. Clinical Practice Guideline for Acute Kidney Injury. Kidney Int 2012; 2(suppl): 1-138. Disponível em: https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf.

4. Veronese FV, Manfro RC, Thomé FS, Barros E. Nefrologia na Prática Clínica. São Paulo: Livraria Balieiro; 2019. 880p.

5. Ince C. The microcirculation is the motor of sepsis. Critical Care 2005;9(Suppl 4):S13-S19. Disponível em: http://dx.doi.org/10.1186/cc3753.

6. Zhang CF, Wang HJ, Tong ZH, Zhang C, Wang YS, Yang HQ et al. The diagnostic and prognostic values of serum and urinary kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin in sepsis induced acute renal injury patients. Eur Rev Med Pharmacol Sci 2020 May;24(10):5604-5617. Disponível em: http://dx.doi.org/10.26355/eurrev_202005_21346.

7. Wu Q, Xiao Z, Pu Y, Zhou J, Wang D, Huang Z et al. TnI and IL-18 levels are associated with prognosis of sepsis. Postgrad Med J 2019 May;95(1123):240-244. Disponível em: https://doi.org/10.1136/postgradmedj-2018-136371.

8. Leem AY, Park MS, Park BH, Jung WJ, Chung KS, Kim SY et al. Value of Serum Cystatin C Measurement in the Diagnosis of Sepsis-Induced Kidney Injury and Prediction of Renal Function Recovery. Yonsei Med J 2017 May;58(3):604-612. Disponível em: https://doi.org/10.3349/ymj.2017.58.3.604.

9. Tanabe J, Ogura Y, Nakabayashi M, Nagai Y, Watanabe S, Sugaya T et al. The Possibility of Urinary Liver-Type Fatty Acid-Binding Protein as a Biomarker of Renal Hypoxia in Spontaneously Diabetic Torii Fatty Rats. Kidney Blood Press Res 2019;44(6):1476-1492. Disponível em: https://doi.org/10.1159/000503926.

10. Endre ZH, Westhuyzen J. Early detection of acute kidney injury: emerging new biomarkers. Nephrology (Carlton) 2008;13(2):91-8. Disponível em: https://doi.org/10.1111/j.1440-1797.2007.00905.x.

11. De Oliveira Neves FM, Araújo CB, Freitas DF, Arruda BFT, Macêdo Filho LJM, Salles VB et al. Fibroblast growth factor 23, endothelium biomarkers and acute kidney injury in critically-ill patients. J Transl Med 2019;17(121). Disponível em: https://doi.org/10.1186/s12967-019-1875-6.

12. Kashani K, Khafaji AA, Ardiles T, Artigas A, Bagshaw SM, Bell M et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Critical Care 2013;17(1):R25. Disponível em: https://doi.org/10.1186%2Fcc12503.

13. Cruz J, Cruz HMM, Kirsztajn GM, Oliveira RB, Barros RT. Atualidades em Nefrologia 15. São Paulo: Sarvier; 2018. 459p.

14. Jiang L, Xu L, Mao J, Li J, Fang L, Zhou Y et al. Rheb/mTORC1 signaling promotes kidney fibroblast activation and fibrosis. J Am Soc Nephrol 2013; 24(7):1114-26. Disponível em: https://doi.org/10.1681/asn.2012050476.

15. Lazo-Fernández Y, Baile G, Meade P, Torcal P, Martínez L, Ibanez C et al. Kidney-specific genetic deletion of both AMPK α-subunits causes salt and water wasting. Am J Physiol Renal Physiol 2017;312(2):352-365. Disponível em: https://doi.org/10.1152/ajprenal.00169.2016.

16. Iwaki T, Bennion BG, Stenson EK, Lynn JC, Otinga C, Djukovic D et al. PPARα contributes to protection against metabolic and inflammatory derangements associated with acute kidney injury in experimental sepsis. Physiol Rep 2019; 7(10):e14078. Disponível em: https://doi.org/10.14814/phy2.14078.

17. Hu J, Qiao J, Yu Q, Liu B, Zhen J, Liu Y et al. Role of SIK1 in the transition of acute kidney injury into chronic kidney disease. JTranslMed 2021;19(69). Disponível em: https://doi.org/10.1186/s12967-021-02717-5.

18. Chen YT, Tsai TH, Yang CC, Sun CK, Chang LT, Chen HH et al. Exendin-4 and sitagliptin protect kidney from ischemia-reperfusion injury through suppressing oxidative stress and inflammatory reaction. J Transl Med 2013;11(270). Disponível em: https://doi.org/10.1186/1479-5876-11-270.

19. Ying J, Wu J, Zhang Y, Han Y, Qian X, Yang Q et al. Ligustrazine suppresses renal NMDAR1 and caspase-3 expressions in a mouse model of sepsis-associated acute kidney injury. Mol Cell Biochem 2020;464(1-2):73-81. Disponível em: https://doi.org/10.1007/s11010-019-03650-4.

20. Wang AG, Diamond M, Waddell J, MaKenna MC. Effect of Acetyl-L-carnitine Used for Protection of Neonatal Hypoxic-Ischemic Brain Injury on Acute Kidney Changes in Male and Female Rats. Neurochem Res 2019;44(10):2405-2412. Disponível em: https://doi.org/10.1007/s11064-019-02807-3.

21. Hu MC, Shi M, Zhang J, Quinones H, Kuro-o M, Moe OW et al. Klotho deficiency is an early biomarker of renal ischemia-reperfusion injury and its replacement is protective. Kidney Int 2010;78(12):1240-51.
Disponível em: https://doi.org/10.1038/ki.2010.328.

22. Si Y, Bao H, Han L, Shi H, Zhang Y, Xu L et al. Dexmedetomidine protects against renal ischemia and reperfusion injury by inhibiting the JAK/STAT signaling activation. J Transl Med 2013;11(141). Disponível em: http://www.translational-medicine.com/content/11/1/141.

23. Duann P, Li H, Lin P, Tan T, Wang Z, Chen K et al. MG53-mediated cell membrane repair protects against acute kidney injury. Sci Transl Med 2015;7(279):279ra36. Disponível em: https://doi.org/10.1126/scitranslmed.3010755.