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Review article

Urinary Biomarkers as Early Indicators of Acute Kidney Injury in Neonates with Perinatal Asphyxia

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SUMMARY

Introduction/Aim. Perinatal asphyxia (PA) is a condition in which there is a decreased or interrupted blood and oxygen supply to the tissues of the fetus, i.e. the newborn, immediately before, during, or immediately after delivery. It constitutes a significant cause of mortality, accounting for 23-24% of all neonatal deaths. The estimated global incidence of perinatal hypoxia is approximately 0.5% of the total number of live births at gestational age over 36 weeks. PA negatively impacts the entire organism, especially metabolically demanding tissues. Due to the sensitivity of the kidneys to oxygen deprivation, acute kidney injury (AKI) can develop within the first 24 hours of the ischemic episode. Prolonged ischemia may lead to irreversible cortical necrosis. Early recognition of AKI is crucial for adequate fluid and electrolyte replacement, as the action of pre-renal etiological factors is a dynamic process with a reversible onset. However, AKI represents a poor prognostic sign, with higher mortality in neonates who develop AKI after perinatal asphyxia, and up to 40% of survivors may have permanent kidney damage. Given the specificity of both the population and the clinical entity, there is a clear need for newer, more sensitive, and specific biomarkers of renal function. The aim of the paper was to review the most significant urinary biomarkers in neonates with perinatal asphyxia that could be crucial for early detection of renal impairment.
Methods. Analysis of scientific and professional papers published in the last ten years in international scientific and professional journals available in the PubMed database.
Conclusion. When considering a potential biochemical marker, the type of biological sample in which it is quantified is a crucial characteristic that must be taken into account. For newborns, obtaining a sample non-invasively is of utmost importance. In this context, urine analysis emerges as a good choice. Metabolites in the urine of PA patients have been proven significant for monitoring the renal function. Unfortunately, urine as a biological sample has the drawback that it cannot be obtained immediately after birth, and a significant number of neonates due to pre-existing renal damage may be anuric.

Keywords: **perinatal asphyxia, acute kidney injury, urinary biomarkers**

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INTRODUCTION

Asphyxia is a condition in which pulmonary, or in the case of the fetus, placental gas exchange is significantly compromised or completely interrupted. It is a state induced by hypoxia and/or ischemia, associated with lactic acidosis. Hypoxia or anoxia signifies a partial or complete lack of oxygen in tissues or blood. Ischemia represents a reduction (partial ischemia) or cessation (complete ischemia) of circulation in organs, compromising the delivery of oxygen and substrates to tissues (1). Perinatal asphyxia (PA) is a condition in which there is a decreased or interrupted blood and oxygen supply to the tissues of the fetus, i.e. the newborn, immediately before, during, or immediately after delivery. PA is a significant cause of mortality, accounting for 23-24% of all lethal outcomes in the neonatal period. PA negatively impacts the entire organism, especially metabolically demanding tissues of the central nervous system, heart, kidneys, and gastrointestinal tract. It significantly affects the mortality and morbidity of newborns. The estimated global incidence of perinatal hypoxia is approximately 0.5% of the total number of live births at gestational age over 36 weeks (2).

PA can result from maternal conditions (severe anemia, severe hypoxia, pre-eclampsia and eclampsia, trauma, shock, coagulation disorders), various pathological conditions of the fetus/newborn (cyanogenic heart defects, persistent pulmonary hypertension of the newborn, cardiomyopathy, shock of various etiologies, fetal hydrops, infections, coagulopathies), complications related to the placenta and umbilical cord (placental abruption, placenta previa, umbilical cord knot), but it can also be idiopathic (3).

Hypoxia triggers complex reflex responses aimed at redirecting blood to priority organs—the brain, heart, and adrenal glands, at the expense of other organs. Since the kidneys are very sensitive to oxygen deprivation, acute kidney injury (AKI) can develop within the first 24 hours of the ischemic episode. If ischemia is prolonged, irreversible cortical necrosis may occur. Early recognition of AKI is crucial for adequate fluid and electrolyte replacement, as the action of pre-renal etiological factors is a dynamic process with a reversible onset. However, AKI represents a poor prognostic sign. Mortality is higher in neonates who develop AKI after perinatal asphyxia, and up to 40% of survivors may have permanent kidney damage (1, 4).

Clinical-biochemical criteria for defining renal damage in neonates exposed to PA are inconsistent. According to the study by Shah et al. (5), these are: anuria or oliguria (< 1 mL/kg/h) for 24 hours or longer with serum creatinine values >100 μmol/L; or anuria/oliguria for 36 hours; or any serum creatinine value >125 μmol/L; or multiple serial measurements indicating postnatal increase in creatinine values.

Given the specificity of both the population and the clinical entity, there is a clear need for newer, more sensitive, and specific biomarkers of renal function. When considering a potential biochemical marker, the type of biological sample in which it is quantified is a crucial characteristic that must be taken into account. For newborns, obtaining a sample non-invasively is of utmost importance. In this context, urine analysis emerges as a good choice. Metabolites in the urine of PA patients have been proven significant for monitoring the renal function. Unfortunately, urine as a biological sample has the drawback that it cannot be obtained immediately after birth, and a significant number of neonates due to pre-existing renal damage may be anuric (6).

AIM

The aim of the paper was to review the most significant urinary biomarkers in neonates with perinatal asphyxia that could be crucial for early detection of renal impairment through the analysis of scientific and professional papers published in the last ten years in international scientific and professional journals available in the PubMed database.

Cystatin-C (CysC)

CysC is a low-molecular-weight protein with a mass of 13 kDa produced by nucleated cells, functioning as a protease inhibitor. It is excreted by the kidneys through glomerular filtration, but it is not present in significant quantities in urine because proximal tubular cells almost completely absorb it (7). CysC does not cross the hematoplacental barrier, making it a significant indicator of renal function in newborns in the early postnatal period. It is superior to creatinine, which crosses the hematoplacental barrier and, therefore, cannot detect antenatal kidney damage, as maternal kidneys can clear the fetal creatinine. Since it is almost entirely reabsorbed,

serum CysC values cannot be considered a direct marker of renal damage but rather an indicator of changes in glomerular filtration rate. In contrast, urinary CysC values are a direct indicator of proximal tubular damage (7, 8).

Li et al. (9) identify urinary CysC as significant for detecting renal damage and predicting AKI in neonates with confirmed perinatal asphyxia. Sarafidis et al. (10) demonstrated that serum CysC values were elevated in neonates only on the first day after the asphyctic episode compared to the control group, while urinary CysC values were elevated on the first, third, and tenth day. Khosravi et al. (11) state that in their study of 55 patients diagnosed with AKI in the neonatal intensive care unit, CysC values had predictive significance for the development of AKI with sensitivity of up to 98.2%. Additionally, CysC values correlate with the severity of hypoxic ischemic encephalopathy (HIE). Studies on the utility of CysC in clinical practice conducted on an older population are not relevant in neonatology, as urinary CysC values change over time, decreasing with kidney maturation (12).

Neutrophil gelatinase–associated lipocalin (NGAL)

Neutrophil gelatinase–associated lipocalin (NGAL) is a protein with a mass of 21 kDa that represents lipocalin 2 or siderocalin covalently bound to the gelatinase of neutrophil granulocytes. It is released by specific granules of neutrophil granulocytes after activation. The values of this biomarker are elevated in the serum and urine of patients with tubular damage (13). Animal models have confirmed that it is one of the earliest detectable proteins in serum and urine in the case of ischemic kidney damage (14). After ischemia-reperfusion injury, the kidney responds within the first 30 minutes by releasing large amounts of NGAL into the urine through the epithelial cells of the tubules. Due to this fact, NGAL is also referred to as the "renal troponin," alluding to the role of troponin as a diagnostic and prognostic marker in acute coronary syndrome (15, 16).

In a prospective study by Kari et al. (17), a six–fold increase in NGAL in the urine of patients with AKI was observed two days before the rise in serum creatinine values. Sarafidis et al. (10) prospectively monitored the role of NGAL in detecting post–asphyctic AKI and found an increase in this marker compared to the control group on the first, third, and tenth day. It is particularly significant that the increase in NGAL was detected before the rise in serum creatinine values in these patients. Zhang et al. (18) even confirmed elevated NGAL values in the urine of neonates who experienced moderate intrauterine asphyxia, while serum creatinine and urea values were not elevated in these patients compared to the control group. The use of this marker can enable the early initiation of supportive therapy for these patients and improve survival prospects. Although numerous studies have shown that this biomarker has clinical utility in patients with post–asphyctic kidney damage, authors have not reached a consensus on the cutoff values for this parameter (19).

Kidney injury olecule 1 (KIM-1)

KIM-1 is a transmembrane glycoprotein with a mass of 104 kDa expressed by the proximal tubule cells of the kidney. Its particular significance lies in the fact that it cannot be detected under physiological conditions, and it is only excreted in urine after exposure of the kidneys to ischemia or toxins (20, 21). Previous research has shown that KIM-1 concentration in urine is highest in kidney damage resulting from ischemia, which is precisely the pathophysiological mechanism of renal damage in perinatal asphyxia. KIM-1 stands out from other biomarkers considering that it can be detected in urine as early as 5-6 hours after tubular cell damage (22-25). In a prospective study from 2022, Rumpel et al. (24) demonstrated that KIM-1 plays a significant role in predicting AKI in neonates diagnosed with HIE. In this study, KIM-1 had better predictive power compared to CysC and NGAL, but the authors note that, although statistically significant, KIM-1 has average specificity and sensitivity. Apart from this study, further data on the clinical utility of this marker in patients with PA are insufficient. However, there are studies on KIM-1 in the urine of pediatric patients with conditions that physiologically correspond to kidney damage in PA, i.e. renal ischemia. Assadi et al. (5) showed that urinary KIM-1 values can significantly contribute to the early detection of kidney damage in pediatric patients with circulatory collapse due to hypovolemic, cardiogenic, and distributive shock. A rapid test for detecting the ectodomain of KIM-1 in urine has been developed recently, requiring only 30 μL of the sam-

ple and providing results within 15 minutes, significantly facilitating its use in everyday clinical and biochemical practice (6).

Interleukin 18 (IL-18)

IL-18, formerly known as interferon-gamma-inducing factor, is a proinflammatory cytokine with a molecular mass of 18 kDa. Urinary IL-18 plays a crucial role in the inflammation of the renal interstitium, infiltration of neutrophil granulocytes and macrophages, and apoptosis of tubular cells (26). It represents an early, non–invasive biomarker of AKI. Its values are much more significant in acute kidney conditions compared to other renal diseases. As an early diagnostic marker, urinary IL-18 has sensitivity and specificity of over 90% (27, 28). It is synthesized in an inactive form and gets activated by the action of caspase-1 in the epithelial cells of proximal tubules. Its presence in urine indicates ischemic tubular necrosis, which has been confirmed in animal models. However, the exact mechanism of renal damage through the action of IL-18 is still insufficiently known (26).

In a prospective study from 2016, Oncel et al. (29) found that IL-18 values were significantly higher in neonates with asphyxia compared to the control group, as well as in asphyxiated neonates with AKI compared to asphyxiated neonates without AKI. In a sample of 105 neonates with perinatal asphyxia, Essajee et al. (30) found significantly higher values of urinary IL-18 in neonates with AKI. In a prospective study from 2022, Rumpel et al. (23) detected urinary IL-18 as a biomarker with predictive significance for the development of AKI among newborns with HIE undergoing therapeutic hypothermia. Apart from this study, it is not known that other authors have quantified IL-18 in the urine of neonates with HIE. The sample of interest in this population is mainly serum (31).

β2-Microglobulin (β2M)

β2M is a low-molecular-weight protein with a mass of 11.8 kDa that is filtered in the glomeruli of the kidneys and then completely absorbed by proximal tubular cells through endocytosis (32). Elevated levels of this biomarker are indicative of damage to proximal tubular cells. In cases of acute kidney injury due to ischemia, β2M can be detected in the urine within 48 hours of the onset of ischemia (32, 33). One limitation of this biomarker is that it degrades in acidic urine, so it is recommended that patients receive bicarbonates before quantifying this protein to raise the urine pH above 7 (34).

Research by El-Gendy et al. (35) suggests that urinary β2M levels serve as an indicator of renal insult with high specificity and sensitivity in neonates with perinatal asphyxia. In a prospective study with 80 term newborns with perinatal asphyxia, Abdullah et al. (36) identified β2M as an early biomarker of kidney damage. Mehrkash et al. (37) discovered significantly elevated levels of urinary β2M in neonates with perinatal asphyxia compared to the control group. The study also revealed significantly higher urinary β2M levels in neonates with perinatal asphyxia who developed acute kidney injury.

CONCLUSION

The mentioned biomarkers have demonstrated significance in individual studies, but further research in this field is necessary to confirm their use as clinically reliable indicators of kidney damage in newborns with diagnosed perinatal asphyxia. The absence of the exact "cut-off" values is making interpretation of results complicated, which is something that needs to be addressed in further research. Until then, a simultaneous use of multiple biomarkers could improve diagnostic sensitivity. Additionally, from a biochemical laboratory perspective, it is essential to find simpler and more accessible methods for their determination.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Review article

Urinarni biomarkeri kao rani pokazatelji akutnog oštećenja bubrega kod novorođenčadi sa perinatalnom asfiksijom

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SAŽETAK

Uvod/Cilj. Perinatalna asfiksija (PA) je stanje u kojem je neposredno pre, u toku ili neposredno nakon porođaja smanjen ili prekinut dotok krvi i kiseonika u tkiva fetusa, tj. novorođenčeta, te stoga predstavlja značajan uzrok mortaliteta i čini 23%–24% svih letalnih ishoda u neonatalnom periodu. Procenjena incidencija perinatalne hipoksije na globalnom nivou iznosi oko 0,5% od ukupnog broja živorođene dece gestacijske starosti preko 36 nedelja. PA ima negativan uticaj na čitav organizam, a posebno na tkiva koja su metabolički veoma zahtevna. Kako su bubrezi veoma osetljivi na deprivaciju kiseonika, akutno bubrežno oštećenje (ABO) može se razviti već u prva 24 sata od početka ishemične epizode. Ukoliko se ishemija prolongira, može doći i do ireverzibilne kortikalne nekroze. Rano prepoznavanje ABO-a je veoma važno radi adekvatne nadoknade tečnosti i elektrolita jer delovanje prerenalnih etioloških faktora predstavlja dinamičan proces čiji je početak reverzibilan. Ipak, ABO predstavlja loš prognostički znak. Mortalitet je veći kod neonatusa koji nakon perinatalne asfiksije razviju i ABO, a čak do 40% preživelih može imati trajno oštećenje bubrega. Imajući u vidu specifičnosti, kako populacije tako i samog kliničkog entiteta, jasna je potreba za novijim, senzitivnijim i specifičnijim biomarkerima bubrežne fukcije. Cilj ovog rada bio je pregled najznačajnijih urinarnih biomarkera kod novorođenčadi sa perinatalnom asfiksijom, koji bi mogli biti ključni za rano otkrivanje oštećenja bubrega.
Metode. Analizirani su naučni i stručni radovi objavljeni u poslednjih 10 godina u međunarodnim naučnim i stručnim časopisima dostupnim u bazi podataka *PubMed*.
Zaključak. Kada se razmatra potencijalni biohemijski marker, vrsta biološkog uzorka u kojem se isti kvantifikuje jedna je od glavnih karakteristika koja se mora uzeti u obzir. Za novorođenčad je od izuzetnog značaja da dobijanje uzorka bude neinvazivno. Imajući to u vidu, analiza urina se nameće kao dobar izbor. Metaboliti u urinu pacijenata sa PA dokazano su značajni za praćenje renalne funkcije. Nažalost, nedostatak urina kao biološkog uzorka ogleda se u nemogućnosti dobijanja uzorka odmah nakon rođenja, a značajan broj neonatusa usled već postojećeg renalnog oštećenja može biti anuričan.

Ključne reči: **perinatalna asfiksija, akutna bubrežna insuficijencija, urinarni biomarkeri**