SIGNIFICANCE OF FIBROBLAST GROWTH FACTOR 23 IN ACUTE KIDNEY INJURY

Sanja Sakan[1], Nikolina Bašić-Jukić[2], Petar Kes[2], Bojan Jelaković[2], Daniela Bandić Pavlović[3] and Mladen Perić[3]

[1]Department of Anesthesiology and Intensive Care, Jordanovac Clinical Department of Thoracic Surgery; [2]Clinical Department of Nephrology, Arterial Hypertension and Dialysis; [3]Clinical Department of Anesthesiology, Resuscitation and Intensive Care, Zagreb University Hospital Center, Zagreb, Croatia

SUMMARY – Acute kidney injury is a clinical syndrome associated with increased patient morbidity and mortality, as well as serious short-term and long-term consequences, especially in the perioperative period. Yet, patients having suffering from temporary acute kidney injury and achieving full recovery of kidney function usually complain of poor quality of life associated with loss of energy and limited physical activity. Therefore, there is a necessity for a novel biomarker of acute kidney injury with better features than currently used serum creatinine and urine output. So far, several investigations have demonstrated that the fibroblast growth factor 23 could be that desperately searched novel biomarker of acute kidney injury. It cannot only detect kidney dysfunction at the time but also before the injury process begins. Moreover, serum levels of the fibroblast growth factor 23 can predict adverse progression of the kidney injury. However, the role of the fibroblast growth factor 23 in the acute but also in chronic kidney dysfunction is still a riddle that requires additional research to clarify it.

Key words: *Acute kidney injury; Biological biomarkers; Fibroblast growth factor 23; Perioperative period*

Acute Kidney Injury

Acute kidney injury (AKI) is a frequent perioperative complication and when it occurs independently, it increases patient morbidity, mortality and poor outcome[1-4]. AKI is a clinical syndrome characterized by a sudden or persistent decrease in kidney function[5-9]. Due to reduction in the glomerular filtration rate (GFR), it is usually manifested as an increase in serum creatinine or decrease in urine output. Although GFR is the accepted indicator of renal function, due to its difficult measurement it is usually assessed from serum creatinine levels and urine output[10]. However, elevation of serum creatinine and decrease in urine output do not allow clinicians to make a timely diagnosis of AKI, or to detect the site or severity of injury[11]. Serum creatinine is a renal biomarker the values of which vary widely with the patient clinical condition and therapy; thus, elevation in serum creatinine is usually delayed by several hours and occasionally by several days until reaching a steady value[12]. Also, about 50% of renal function must be lost prior to serum creatinine starting to rise[12]. On the other hand, diuresis is not a sensitive renal biomarker because many hospitalized patients, especially critically ill, receive diuretics in their daily therapy, so oliguria cannot be detected[12]. In addition, great attention should be paid to surgical patients that usually develop temporary oliguria postoperatively due to perioperative multifactorial and complex hemodynamic and volume

Correspondence to: *Sanja Sakan, MD*, Department of Anesthesiology and Intensive Care, Jordanovac Clinical Department of Thoracic Surgery, Zagreb University Hospital Center, Jordanovac 104, HR-10000 Zagreb, Croatia
E-mail: sanja.sakan@hotmail.com

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disturbances, which lead to hypovolemia and subsequent renal hypoperfusion[13-16]. It is considered as a normal physiological renal response, so a clinician has to distinguish it from AKI.

Kidney is a robust organ and can put up with exposure to many noxious impacts without any significant structural and functional renal impairment[10]. However, when this renal impairment does occur, it usually implies that severe multiorgan derangements have happened and that the patient's condition is rather serious. Every clinician should be aware of a timely narrow therapeutic window of 24-48 hours between kidney submission to the high risk and noxious factors, and AKI genesis. In this important period, preventive and supportive measures must be undertaken and a novel biomarker of AKI should demonstrate its sensitivity and specificity. Therefore, small changes in serum creatinine values and urine output are independently associated with mortality and should be early detected and alert every clinician to start appropriate patient monitoring and therapy[17-20]. Many studies have shown that even acute and mild kidney dysfunction can have severe sequels[5-9]. Moreover, 30% of patients who have experienced temporary uncomplicated AKI with full recovery of kidney function are at an increased risk of chronic kidney disease (CKD) development[19,20,21].

The etiology and pathophysiology of AKI are complex and multifactorial[22-24]. Nevertheless, we can conclude that the major kidney risk factors are hypotension, ischemia and reperfusion, inflammation and nephrotoxins[23,24]. Their detrimental impact on the kidney function and structure can be reversible, especially if therapeutic measures are applied in the narrow therapeutic renal window. Thereby, the main goal is to detect every insult to the kidney as early as possible. Therefore, a novel AKI biomarker is required. Till then, AKI should be always if possible predicted by the clinician and a supportive and nephroprotective strategy should be initiated[13]. These measures consist of optimization of hemodynamic parameters like maintaining systolic pressure >80 mm Hg, mean arterial pressure >65 mm Hg and renal perfusion pressure[13]. However, we consider that optimization of hemodynamic parameters is best managed by timely and early goal directed therapy using less invasive hemodynamic monitoring if possible[13]. Another puzzle in daily management of AKI is when to initiate the supportive renal replacement therapy. Nowadays, there is still a tendency to postpone renal replacement therapy as long as possible[10]. Renal replacement therapy deferring is usually justified by the patient hemodynamic instability, dialysis catheter associated complications, and activation of the patient immune and inflammation system due to bioincompatible dialysis membrane[25,26]. However, studies have demonstrated that late renal replacement therapy initiation is connected with increased patient mortality, longer duration of renal replacement therapy and hospital stay, compromised recovery of renal function, and in the end with a greater risk of progression to CKD and dialysis dependence[27-31]. On the other hand, early initiation of renal replacement therapy as soon as the patient develops stage 3 of AKI according to the RIFLE criteria is warranted by the benefit of avoiding exposure to the deleterious effects of metabolic waste products and abnormalities, or volume overload[10]. The major goal of the novel kidney biomarker would be to predict renal recovery and to give clear answer to the relevant question when to initiate and discontinue renal replacement therapy[10]. By then, renal replacement therapy initiation will remain a clinical risk-benefit ratio decision based on the already developed complications manifested in the fluid, metabolic and electrolyte system of the individual patient[10].

Thus, the desperately needed novel kidney biomarker should have the ability to early diagnose and predict the AKI course, identify the etiology, location and severity of renal injury, provide individual patient risk stratification, define timing of renal replacement therapy initiation and discontinuation, and to be cost-effective, reliable and easy to use in clinical practice[11,32,33].

Fibroblast Growth Factor 23

Fibroblast growth factor 23 (FGF23) is a bone produced novel hormone that for now has excellent features to be considered a new and early AKI biomarker[34]. It is generated and secreted primarily in bones by osteoblasts and osteocytes[35]. It pertains to the FGF19 subfamily and acts as an endocrine phosphaturic hormone, i.e. phosphatonine[36]. So, the major physiological role of FGF23 is to maintain phosphate homeostasis[37]. Preserving the systemic phosphate ho-

meostasis is essential for the body. The reason is that various cellular functions ranging from cellular signaling to enzymatic activities depend on the phosphate balance[38]. When this balance is disrupted, severe vital organ system malfunctions arise[38]. Kidney is the organ responsible for preserving phosphate homeostasis by a closed negative feedback loop between the kidneys, bones and parathyroid glands. When this loop becomes open, serum phosphate levels start to increase. So, hyperphosphatemia increases parathyroid hormone (PTH) and FGF23 secretion, which in turn enhance phosphaturia in a similar manner. As a result of kidney dysfunction, this negative feedback system is disrupted and phosphate serum levels augmentation continues. The only difference between PTH and FGF23 is that PTH increases phosphaturia in a few hours, whereas FGF23 reacts after several days[39,40]. The main phosphaturic mechanism of FGF23 is performed by inhibiting renal tubular reabsorption of phosphate by reducing the number of sodium-dependent phosphate IIa and IIc cotransporters in the apical brush border of the renal proximal tubule[41-43]. Everything we currently know about the FGF23 intracellular mechanism of action on renal phosphate excretion is that it has to connect with its main renal specific receptor FGFR1 together with the help of the Klotho transmembrane protein as a coreceptor to accomplish the effect[41,42]. Hence, the Klotho protein is the relevant factor that determines the FGF23 effects on target organs such as the kidney, parathyroid glands, pituitary gland and choroid plexus in the brain[44]. Moreover, other avenues of maintaining phosphate homeostasis are decreasing intestinal phosphate absorption through direct action of reducing the number of sodium-dependent phosphate IIb cotransporters in the gastrointestinal mucosal apical border, and indirectly through blocking calcitriol synthesis by reducing renal 1-alfa-hydroxylase activity and enhancing calcitriol catabolism by stimulating 24-alfa hydroxylase activity[34,36,45]. The sequel of this avenue is diminished vitamin D-dependent intestinal phosphate absorption[45]. However, the FGF23 fashion of degradation is not well understood[46]. According to the literature, there are two forms of circulating FGF23 in the serum. One is intact and full-length form of the FGF23 which has biological activity and the other is inactive C-terminal fragment of the FGF23 without biological activity in the serum[36]. The assessed half-life of the intact FGF23 in the circulation is about 58 minutes[47].

Fibroblast Growth Factor 23 and Chronic Kidney Disease

Studies of the FGF23 in patients suffering from CKD have revealed that the capital drivers for the increased FGF23 production are intestinal phosphate absorption after high oral phosphate entry, calcitriol, and PTH directly and indirectly by increased 1,25-dihydroxy vitamin D3-dependent production[36,48-51]. Thus, FGF23 serum levels already significantly start to rise during early stages of CKD before serum phosphate derangements can be detected[46,52,53]. Thereby, in patients with end-stage CKD, they are hundreds-to thousands-fold higher than normal values[46,52,53]. Hence, we conclude that FGF23 could be the early biomarker of renal deterioration in the progress of CKD, and its serum values can predict the CKD outcome[36]. Also, FGF23 increased serum values are independently associated with higher mortality, therapy resistant secondary hyperparathyroidism, left ventricular hypertrophy and cardiovascular mortality in CKD patients[38,52]. This adverse effect of elevated FGF23 serum concentrations on cardiovascular system is not well understood. Some evidence supports direct FGF23 toxicity on the cardiac and vascular endothelial function through low-affinity Klotho independent FGF receptors[54,55]. Other evidence demonstrates the FGF23 cardiovascular toxicity due to disruption in the calcium-phosphate metabolism homeostasis[36]. However, regardless of the mechanism of action, the result is the same.

Fibroblast Growth Factor 23 and Acute Kidney Injury

There are not so many studies on the role of FGF23 in AKI, but recent studies have revealed that AKI is associated with raised serum levels of FGF23[56-60]. In addition, studies showed that elevated serum levels of FGF23 in AKI patients were connected with unfavorable outcome in terms of a significantly increased risk of death or need of renal replacement therapy[57,58]. Serum levels of FGF23 in AKI rise independently of the already mentioned drivers in CKD patients such as high

oral phosphate entry, calcitriol and PTH[57]. However, the precise mechanism of the increased FGF23 levels has not yet been elucidated. Increased production rather than decreased elimination of FGF23 contributes to elevated levels of FGF23 in AKI, so impaired renal FGF23 scavenging due to reduction of the glomerular function units is not the major pathway for raising the FGF23 levels[61]. Also, another pathway that can contribute to FGF23 serum elevation may be deficiency of the important FGF23 coreceptor Klotho in the injured kidney[62]. The Klotho deficiency leads to the FGF23 resistance resulting in raised FGF23 serum levels. Besides, enhanced bone production of FGF23 in AKI patients was demonstrated by immunohistochemical and Western blot analyses of the bones also as a mechanism contributing to elevated FGF23 serum levels[63,64]. Yet, the responsible kidney driven factor for increased FGF23 bone production and the actual pathway of interaction in this novel bone-kidney axis still remains obscure[36]. In addition, due to many difficulties in detecting AKI in perioperative settings, FGF23 manifested as a reliable biomarker of the acute kidney dysfunction since it begins to rise significantly within 24 hours postoperatively[57]. Furthermore, one pilot study in pediatric population submitted to cardiac surgery indicated that elevated preoperative FGF23 serum levels were also associated with a two-fold increased risk of AKI development, yet correlating with positive fluid balance, length of mechanical ventilation, and length of stay at the intensive care unit[57].

Conclusion

In conclusion, the currently used kidney injury biomarkers cannot detect AKI timely and usually their concentrations start to rise when the injury process is in the late phase. The goal of the new and early kidney injury biomarker is to predict and diagnose AKI with the aim to start the nephroprotective treatment before the damage has happened. FGF23 could be a novel promising biomarker of AKI, especially in the complex perioperative period. However, additional research in the field is needed.

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Sažetak

ULOGA ČIMBENIKA RASTA FIBROBLASTA 23 U AKUTNOJ OZLJEDI BUBREGA

S. Sakan, N. Bašić-Jukić, B. Jelaković, P. Kes, D. Bandić-Pavlović i *M. Perić*

Akutna ozljeda bubrega je klinički sindrom povezan s povišenim rizikom pobola i smrtnosti te kratkotrajnim i dugotrajnim posljedicama, osobito kod bolesnika u perioperacijskom razdoblju. Zbog toga potreban je novi biomarker akutne bubrežne ozljede, bolje specifičnosti i osjetljivosti od serumske vrijednosti kreatinina i diureze. Nekoliko dosadašnjih radova je pokazalo da čimbenik rasta fibroblasta 23 može pravodobno prepozanti poremećaj bubrežne funkcije tijekom samog procesa oštećenja. Također, povišene serumske vrijednosti čimbenika rasta fibroblasta 23 mogu upozoriti na nepovoljan ishod bubrežne ozljede. Međutim, uloga čimbenika rasta fibroblasta 23 u akutnoj bubrežnoj ozljedi je velika nepoznanica te su potrebna daljnja istraživanja.

Ključne riječi: *Akutna ozljeda bubrega; Biološki biljezi; Čimbenik rasta fibroblasta 23; Perioperacijsko razdoblje*