Review Article

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Cofilin-1 as a potential biomarker to evaluate acute kidney injury

Akut böbrek hasarının değerlendirilmesinde potansiyel biyobelirteç olan Cofilin-1'in incelenmesi

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Abstract: Acute kidney injury (AKI) is a worldwide health problem and defined by rapid loss of excretory function of the kidney with the accumulation of metabolic end products. For effective treatment and prevent complications the early diagnosis of AKI is crucial. The current analytes used to diagnose AKI are not adequately sensitive and specific and therefore clinicians need new biomarkers. One of the new promising biomarker candidates of renal injury is cofilin-1. Previously, in our laboratory we isolated cofilin-1 in kidney preservation solution prior to transplantation and attempted to measure serum cofilin-1 in renal transplanted patients. However, cofilin-1 was not accurately measured in serum samples due to the methodological issues. In this mini-review, we summarized the current knowledge and concepts both in the literature and our experiences with cofilin-1 as a potential biomarker for the diagnosis and management of AKI.

Keywords: Cofilin-1; Biomarker; Acute kidney injury; Renal transplantation; Kidney preservation solution.

Öz: Akut böbrek hasarı dünya genelinde yaygın görülen bir sağlık sorunudur ve metabolik son ürünlerin birikimi ile böbreğin boşaltım işlevini hızlı bir şekilde kaybetmesiyle nitelendirilmektedir. Etkin tedavi ve komplikasyonları önlemek için akut böbrek hasarının erken teşhisi önemlidir. Akut böbrek hasarını teşhis etmek için kullanılan mevcut analitler yeterince hassas ve özgün değildir. Bu nedenle klinisyenlerin yeni biyobelirteçlere ihtiyacı vardır. Böbrek hasarı için umut veren yeni biyobelirteç adaylarından biri cofilin-1'dir. Daha önce laboratuvarımızda, transplantasyon öncesi böbrek koruma solüsyonunda cofilin-1 proteinini izole ettik ve böbrek nakli yapılan hastalarda serum cofilin-1 proteinini ölçmeye çalıştık. Ancak, serum örneklerinde cofilin-1 proteini metodolojik problemlerden dolayı doğru olarak ölçülmedi. Bu mini derlemede, akut böbrek hasarının teşhisi ve tedavisi için cofilin-1 ile ilgili hem literatür bilgisini hem de kendi deneyimlerimizi özetledik.

Anahtar kelimeler: Cofilin-1; Biyobelirteç; Akut böbrek hasarı; Renal transplantasyon; Böbrek koruma solüsyonu.

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Introduction

Acute kidney injury (AKI) is broadly defined as the rapid decrease in glomerular function [1] and therefore it is characterized by rapid loss of excretory function of the kidney with the accumulation of metabolic end products (urea, creatinine and other various waste products) [2]. AKI is a worldwide common health problem and its incidence is increasing rapidly, particularly in patients with acute illness. According to the data of 312 cohort studies obtained from 49 million patients, AKI occurs in one in three children and one in five adults hospitalized with acute illness [3]. Various factors such as old age, diabetes mellitus, hypertension, major surgery, preexisting kidney diseases and cardiovascular diseases increase the incidence of AKI [1]. It is a life-threatening serious condition and associated with high mortality and morbidity rates, chronic and end-stage renal diseases. Therefore, the early diagnosis of AKI is crucial for effective treatment and also to prevent possible complications.

Elevated serum urea and creatinine concentrations are the standard laboratory diagnostic biochemical tests of AKI. However these two waste products are neither sensitive nor specific to AKI. Various factors such as age, sex, muscle mass, muscle injury, nutrition and use of steroids, etc. affect serum level of urea and creatinine [2]. More importantly the serum level of these analytes are normal in the early stage of kidney diseases and become abnormal only when glomerular filtration rate (GFR) decreases seriously, such as more than 50% [2, 4]. In addition to elevated serum level of urea and creatinine, albuminuria is an important signal indicating the development of AKI [5]. More interestingly, AKI induces the expression of renal cortical albumin silent gene and then it produces albumin which is accepted as the renal acute stress reactant [6].

Investigation of new more sensitive and specific biomarkers for AKI are crucial in the diagnosis and monitoring of patients. Despite some serious shortcomings, omics technologies are promising the investigation of the new biomarkers in diagnosis and monitoring of AKI. Various biomarkers such as kidney injury molecule-1, neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, IL-18, liver fatty-acid-binding protein and glutathione-S-transferase have been used to evaluate different stages of kidney injuries [2, 7] (Figure 1). However, these molecules are not specific to GFR; they are used in different aspects of kidney injury. For example, NGAL is being used to evaluate tubular stress or injury [2]. Research will continue, until finding more sensitive and specific biomarkers for both diagnosis and monitoring of AKI. One of the new promising biomarker candidates of renal injury is cofilin-1.

In this mini-review, we summarized the current knowledge and concepts both in the literature and our experiences with cofilin-1 as a potential biomarker for the diagnosis and management of AKI. Additionally, we emphasized how important it is to accurately measure molecules that are thought to be potential biomarkers as we faced methodological issues while we measured cofilin-1 in the serum of renal transplanted patients.

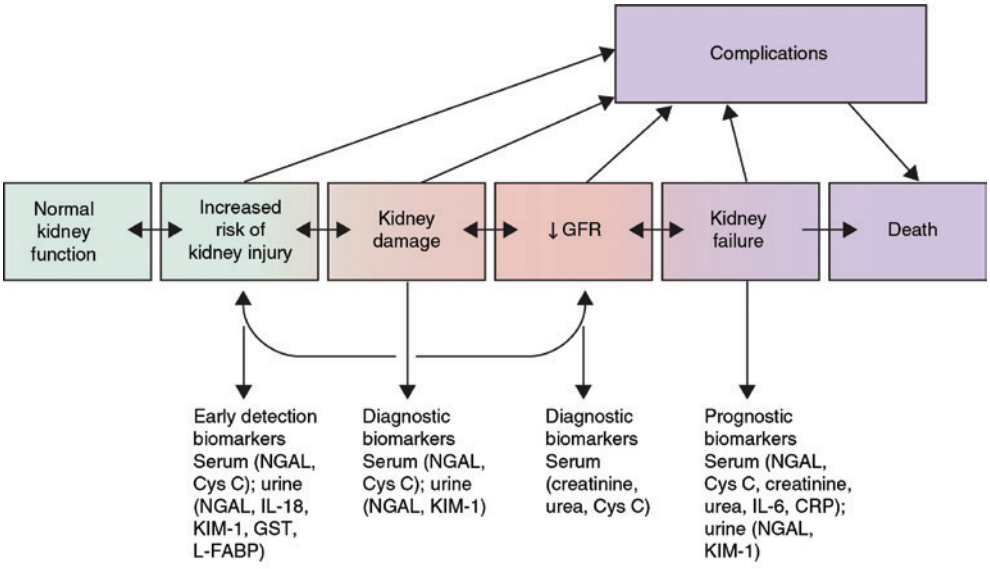

Figure 1: Biomarkers used to evaluate different stages of kidney injuries.
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Cofilin-1

Cofilins are a group of proteins that act in the regulation of actin dynamics. Actin cytoskeletal remodeling is required in response to several cellular and morphological changes including motility, migration, growth, differentiation and cell death [8]. A number of complex signaling pathways and key molecules regulate actin cytoskeleton. For example, several actin-binding proteins are necessary for reorganizing actin cytoskeleton by specifically coordinating the actin assembly and disassembly. In 1980s, Bamburg et al. and Nishida et al. purified a 20 kDa protein from avian and porcine brains that stimulated actin filament depolymerization [9, 10] and was named as cofilin as it builds "cofilamentous structures with actin" [10]. In the next years since the first work on cofilin in porcine brains, several homologues including human [11] and yeast cofilin [12] were identified.

Cofilin, a member of actin regulating proteins, can bind to filamentous (F)-actins and globular (G)-actins. Additionally, cofilin has higher affinity to ADP-bound actin filaments than ATP-bound actin filaments, which then induces the selective disassembly of "aged actin filaments" [13]. Cofilin is required for the physiological function of actin filaments and lack of active cofilin results in limited formation and breakdown of new actin filaments [14].

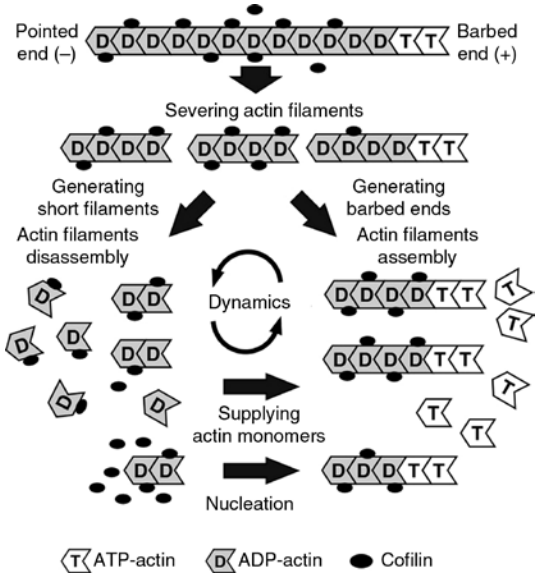

Figure 2: Actin assembly and disassembly by cofilin.
This model asserts that cofilin severs actin filaments by prefentially binding to ADP-bound actin. Depolymerization of these short filaments lead to the regeneration of ATP-bound actin monomers. The regenerated actin monomers have a role in the assembly of the actin cytoskeleton. Reproduced with the permission from Ohashi [18], Copyright 2015, John Wiley and Sons, Inc.

It has been shown that different proteins such as actin interacting protein 1 [15], coronins [16] and twinfilin [17] cooperate with cofilin to enhance and regulate the depolymerization of actin filaments. Additionally, by inducing depolymerization of actin filaments, cofilin also generates free actin monomers for polymerization [13]. This dual effect of cofilin results in enhanced dynamics of actin cytoskeleton (Figure 2).

Mammalian cofilin has three isoforms: actin depolymerizing factor (ADF), cofilin-1 (non-muscle type) and cofilin-2 (muscle type) [19]. ADF is mainly found in endothelial, neuronal and epithelial cells; cofilin-2 in muscle cells but cofilin-1 is ubiquitously expressed and is the major form in non-muscle tissues [19]. The cofilin family members are globular proteins with a core containing four or five b-sheets and encircled by four or five helices [20].

Cofilin-1 seems essential for life and development because cofilin-1 null mice are shown to be embryonic lethal [21]. Gurniak et al. reported that cofilin-1 null mice had defects in the development of neural crest-derived tissues [21]. In addition to its roles in neural tissue and cell development, cofilin-1 plays crucial roles in malignancy [22]. For example, Tsai et al. reported that the growth and invasiveness of non-small cell lung cancer cells in vitro and in a xenograft tumor model were decreased when cofilin-1 is overexpressed [23]. Interestingly, Wang et al. showed epithelial-mesenchymal transition in gastric malignant cells by cofilin-1 due to its roles in cytoskeletal rearrangement [24].

The clinical significance of cofilin-1 has not been evaluated using large scale studies. Recently it has been reported that cofilin-1 might be a biomarker for the evaluation of kidney functions. In our previous study, we isolated cofilin-1 in kidney preservation solutions prior to renal transplantation [25].

Cofilin-1 as a potential biomarker in acute kidney injury

As mentioned above, AKI is broadly defined as the rapid decrease in glomerular functions [1]. The glomerular filtration barrier has three main structures: basement membrane, podocytes and glomerular endothelial cells [26]. The intact cytoarchitecture of podocytes is essential to maintain the glomerular filtration barrier. Podocytes have a complex structure consisting of three different units: cell body, major processes (MP) and foot processes (FP). MPs of podocytes arise from the cell body and split into FPs. The podocytes' FPs are actin based structures [27] and

the regulation of the cytoskeletal structure is a dynamic process which is crucial for well-functioning filtration [28]. Mutations of podocyte proteins lead to reorganization of the cytoskeletal architecture and disruption of the filtration barrier [28]. In podocyte structure and function, cofilin-1 plays an important role as it is an essential regulating factor for the recycling of actin-filaments. This process is necessary to maintain the physiological function of the FP [14] and consequently, cofilin-1 is required for the integrity of podocytes filtration barrier [14]. Additionally, cofilin-1 is required not only for the maintenance and integrity of podocyte architecture but also for the structural changes of actin that occur during induction and recovery from podocyte injuries [29].

The breakdown of podocyte cytoarchitecture results in large-scale proteinuria [30]. Therefore, investigating the molecular pathway regulating this process is essential in understanding the mechanism of proteinuria. The inactivation of cofilin-1 has been suggested to alter the podocyte cytoskeleton organization [31] and decrease the capacity of adaptation to glomerular pressure differences [14] which then results in proteinuria. Therefore, cofilin-1 seems to be a central molecule in the pathophysiology of proteinuric patients.

In addition to proteinuria, cofilin-1 plays important roles in various clinical situations related to renal injuries. In the pathogenesis of hypertensive-induced kidney damage nuclear factor κB (NF-κB) has a crucial function [32] and it has been shown that cofilin-1 is associated with hypertensive nephropathy by regulating the nuclear translocation of NF-κB in the kidney tubular epithelial cells [33].

Renal ischemia has profound effects on cellular junctional complexes, actin architecture and membrane polarity [34]. Ischemia rapidly, even within 5 min, degenerates the architecture of microvillar F-actin [35] and consequently the cell membrane may not be able to maintain its finger-like microvillar structure [34]. Various reports have been shown that in the presence of ischemia, the actin-binding protein family of ADF/cofilin proteins have an important function in the breakdown of apical microvilli structure [36, 37].

Stødkilde et al. have shown that cofilin-1 is upregulated in rats subjected to bilateral ureteral obstruction and they concluded that elevated levels of cofilin-1 increase the ability of the cell to adapt to the increased pressure which may destroy the cell integrity [38]. Elevated levels of cofilin-1 have been reported in nephrogenic diabetes insipidus induced by lithium [39] and hypokalemic nephropathy [40]. Wasik et al. used proteomic techniques and have shown that inactive cofilin-1 is upregulated in diabetic glomeruli suggesting alterations in actin dynamics [41]. Additionally, Chang et al. used gold nanoparticles with an immunoassay approach and detected two fold high cofilin-1 levels in AKI patients compared to the healthy adults [42]. The authors concluded that for the first time it was shown that urinary cofilin-1 was elevated in AKI patients. In summary, all the current findings support the hypothesis that elevated level of cofilin-1 is associated to AKI.

Cofilin-1 in kidney preservation solution

The viability of solid organs are limited to a very short period such as 30–60 min after the disconnection from its native circulation, due to the accumulation of metabolic end products, lack of nutritional substrates and oxygen deficiency [43]. Therefore, the functional preservation of the organ is one of the main issues in solid organ transplantation. Solid organs are preserved within cold preservation solution until its transplantation into the appropriate recipients. Various chemical compounds have been added to the solid organ preservation solution to increase the viability of the organs [44–46]. During preservation period, as a result of tissue injury, various biomolecules including peptides and proteins are released from the organ into the preservation medium. Preservation solution does not only preserve organs prior to transplantation but also become a source of liquid biopsy of transplanted organs. The term ‘liquid biopsy’ refers the molecular analysis of biological fluids and is less invasive in comparison to tissue biopsy [47].

Preservation solutions such as Histidine tryptophane ketoglutarate, University of Wisconsin and Celsior do not contain proteins and peptides and therefore the peptides and proteins isolated from preservation solution are originating from organs. These proteins and peptides provide valuable information about the location of cellular injury. In our previous study, we isolated cofilin-1 from kidney preservation solution and concluded that the presence of cofilin-1 in preservation solutions might be a signal of the cytoskeletal injury during preservation period [25].

From basic research to clinical practice possible biomarkers must pass various steps. In routine practice we use biomarkers in diagnosis, monitoring, screening and case findings. Therefore, well-designed multiple clinical studies are essential to evaluate the strong and weak sides of biomarkers. Isolation of a biomolecule from plasma, blood or other body fluids is not sufficient to evaluate it

in clinical studies. In the first step we should develop reliable methods to measure the biomolecules from plasma or body fluids. In this concept, we decided to measure cofilin-1 level in the serum of kidney transplanted patients after the isolation of cofilin-1 from kidney preservation solution in order to evaluate its clinical significance particularly as a possible biomarker of AKI.

Measurement of cofilin-1 in renal transplanted patients

Up to now various research groups, scientists and organizations have isolated thousands of proteins, peptides and other biomolecules from biological fluids but unfortunately a very small fraction of these biomolecules are being used as clinical biomarkers in medical laboratories. To overcome these problems it is essential to verify the measurement performance of biomarkers by routine methods [such as enzyme-linked immunosorbent assay (ELISA) or chemiluminescence]; otherwise it may not be possible to use these biomarkers effectively in clinical practice. In this regard, we evaluated the clinical significance of cofilin-1, which is proposed to be a potential renal injury biomarker, in renal transplanted patients and healthy subjects.

We measured serum cofilin-1 levels using a quantitative sandwich enzyme immunoassay before the transplantation and 24th, 48th and 96th h following transplantation (Table 1). Additionally, we measured serum urea, creatinine and C-reactive protein levels. The measurement range of cofilin-1 given by the manufacturer was 0.5–10 ng/mL. As shown in Table 1, serum cofilin-1 levels of patients and control subjects were lower than the limit of quantification (LOQ) and consequently we did not make any conclusion about the coffilin-1 level in both renal transplanted and control subjects.

Molecules that are candidates as a new biomarkers have to pass two important stages: accurate measurement and clinical performance. To evaluate a biomarker in clinical studies, in the first line, we have to accurately measure its concentration or activity. For example, if the LOQ of a method is higher than the clinical decision level of the biomarker, we cannot evaluate it in clinical studies. In this case we must give priority to the development of a more sensitive method. Similarly, if the precision and bias of a method is higher than expected then we cannot make our decision reliably due to random and systematic variations. In our experimental approach, we observed the problems mentioned above while measuring serum cofilin-1 in renal transplanted patients using a quantitative sandwich enzyme immunoassay. However, this does not mean that we cannot measure cofilin-1 level in biological samples. There are alternative methods, but these are expensive, time consuming and require qualified staff in biomedical metrology. For example, Chang et al. used a high-throughput localized surface plasmon-coupled fluorescence biosensor technique to measure cofilin-1 in urine samples and they reported the limit of detection of the method for cofilin-1 as 36 pg/mL [42], which is extremely lower than the sandwich enzyme immunoassay (0.5 ng/mL).

Within the last three decades, sophisticated technologies have been used in the measurement of biomolecules. Chemiluminescence methods are reliable, sensitive and easily applicable to automated systems and therefore widely used in medical laboratories. But in the usual, first line of development biomarkers are measured by ELISA not chemiluminescence. Numerous new molecules can be measured by using commercial ELISA methods. Unfortunately most of these methods are not validated correctly and only a few parameters such as precision, carry-over, detection limits and linearity were determined. A careful examination of the procedure of these products shows that even these parameters were not properly assessed.

Table 1: Serum cofilin-1, urea, creatinine and CRP levels of control subjects and renal transplanted patients.[a]

Measurands	Control (n = 17)	Patients (n = 18)			
		BT	24 h[b]	72 h[b]	120 h[b]
Cofilin-1 (ng/mL)	0.26 ± 0.03	0.25 ± 0.04	0.10 ± 0.01	0.09 ± 0.01	0.13 ± 0.01
Urea (mg/dL)	12.8 ± 0.90	66.2 ± 5.16	32.6 ± 2.98	19.9 ± 1.30	22.9 ± 1.59
Creatinine (mg/dL)	0.74 ± 0.04	7.56 ± 0.36	2.48 ± 0.24	1.01 ± 0.05	1.08 ± 0.05
CRP (mg/dL)	0.37 ± 0.08	0.54 ± 0.15	4.93 ± 0.43	1.32 ± 0.18	0.40 ± 0.11

Data are given as Mean ± SE; BT, before transplantation; CRP, C-reactive protein; SE, standard error. [a]The study protocol was approved by the Ethics Committee of Acibadem Mehmet Ali Aydınlar University (ATADEK 2016-3/24), and all subjects provided written informed consent. [b]Measurement time following transplantation.

For example LOQ is not given and coefficient of variation is not properly reported and so on. Furthermore, these products are very expensive in comparison to routine laboratory tests. Reliable measurement procedures remain a big problem in the clinical evaluation of new biomarkers. It is clear that if we want to expedite the clinical evaluation of new biomarkers we should give priority to developing reliable measurements methods.

Conclusion

AKI is a life-threatening condition and its incidence is increasing rapidly particularly in patients with acute illness. The early diagnosis of AKI is crucial for effective treatment and also preventing possible serious complications. However, in laboratory medicine we have limited reliable tests for early diagnosis of AKI and therefore the investigation of new more specific and sensitive biomarkers is crucial in the diagnosis and monitoring of patients. Based on the recent finding published in the literature, one of the new promising biomarker candidates of renal injury is coffilin-1. It is the main component of podocytes and essential for the structural changes of actin filaments that occur during induction and recovery from podocyte injuries.

Before evaluation of cofilin-1 in clinical studies we have to measure its concentration accurately in body fluids. In the present study we have not evaluated all available methods to measure cofilin-1 but if we plan a clinical study about cofilin-1, first of all we should measure and confirm the reliability of cofilin-1 results in intended body fluids.

Although cofilin-1 has an important role in the maintenance of kidney functions, we cannot say that the measured cofilin-1 is tissue specific and originated only from kidneys. In reality all nucleated cells have the potential to synthesize all proteins. In other words kidneys can synthesize various proteins including even albumin [6] and hemoglobin [48].

Conflict of interest statement: The writers declare no conflict of interest.

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