

# Some Biomarkers of Kidney Diseases

## Böbrek Hastalıkları için Bazı Biyobelirteçler

Review Article

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### ABSTRACT

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Kidneys are one of the indispensable organs of our body especially for hemostasis and responsible for regulates arterial pressure, blood filter, water balance, gluconeogenesis etc. Renal diseases have been divided acute kidney injury and chronic kidney diseases according to glomerular filtration rate. At last stage of glomerular filtration rate (5. stage) is not only harmful but also irreversible stage, for overcoming this stage kidney transplant and dialysis are important medical cares. Nowadays biomarkers are useful indicator for diagnostic, therapy and monitoring of diseases control. In this review, some biomarkers were represented and supported by research articles for diagnostic chronic kidney disease with acute kidney injury.

### Key Words

Kidney diseases, biomarkers, BTP, KIM-1, I-18, NGAL, AD, NAG, Albuminuria, L-FABP, cystatin-C

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### ÖZET

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Sunulan bu Özet: Böbrekler vücudumuz için; özellikle hemostaz ve atardamar basıncının düzenlenmesi, kanın temizlenmesi, su dengesi ve glukoneogenez gibi görevlerden sorumlu olan hayati organlardan birisidir. Böbrek hastalıkları glomerüler filtrasyon oranına göre; akut böbrek hasarları ve kronik böbrek hastalıkları olarak 2 gruba ayrılmaktadır. Glomerüler filtrasyon oranının son evresi (5. evre) zararlı olmasının yanında geri dönüşünü olmayan özellikte olup, böbrek nakli ve diyaliz önemli tedavi yöntemleridir. Günümüze biyobelirteçler hastaların teşhisinde, tedavisinde ve hastalığın seyrini takip etmede kullanılırlar. Bu derlemede kronik böbrek hastalıklarını ile akut böbrek hasarlarını teşhis etmek için bazı biyobelirteçler araştırma makaleleri ile birlikte sunulmuştur.

### Anahtar kelimeler

Böbrek hastalıkları, biyobelirteçler, BTP, KIM-1, I-18, NGAL, AD, NAG, Albüminüri, L-FABP, sistatin C

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## INTRODUCTION

Kidneys are retroperitoneal; bean shaped organ that lies body waist (two body side) and covered by fibrous tissue from outside [1,2]. Human kidneys weight is between 115-170 gram, 11-12 cm length, 5-7.5 cm width and 2.5-3 cm thickness but also changes with gender [2]. Nephrons main part of kidneys that is approximately 1 million and has not regenerate ability [3,4]. Lack of regeneration, number of nephrons have been decreasing day by day owing to kidney damage and older age respectively [4].

Main functions of kidneys are to filter blood [1] and remove waste metabolic residues of such as amino acid, nucleic acid, hemoglobin [4], regulates arterial pressure with water balance via Na<sup>+</sup> ions [1,5], stimulates red blood cell productivity for synthesizing erythropoietin [5]. Gluconeogenesis (amino acids and other molecules converted into glucose by kidneys), acid-base balance coordinated with lungs for removing of protein waste residues (sulfuric with phosphoric acids) and regulation of vitamin D with Ca<sup>++</sup> and phosphate ratio with hormones are also controlled by kidneys [5,4].

### Identification of kidney damage

Kidney disease has divided into 2 groups acute kidney injury (AKI) and chronic kidney disease (CKD) [6]. Acute kidney disease is directly measurement of urea with electrolyte levels and determined to decrease of kidney function last 48 hours with serum creatinine level last 6 hours [6]. Chronic kidney disease decorates kidney functions with structure, shows progressive and irreversible effects [6,7]. Some factors triggers kidney disease (especially chronic kidney disease) such as genetically factors related to Alport's or polycystic kidney disease, ethnicity, age, genetic disease, some drugs (anti-inflammatory, penicillin) and streptococcus infection [8]. Beside triggered factors; long term studies shows that chronic kidney disease affected by cardiovascular disease, hypertension, diabetes, HIV, hepatic B and C infections [8,9].

Renal clearance is the filtration rate of some specific exogenous and endogen substances in plasma per minute and formulized according to this equation [10,11].

$$C_m = (U_m \times V) / P_m$$

$C_m$  is the quantity of filtered substance in plasma per unit,  $U_m$  substance level in urea,  $P_m$  substance level in plasma and  $V$  is the urine volume.

Glomerulus filtration rate (GFR) is filtration of some substances from blood (<sup>48</sup>Cr-EDTA, inulin, <sup>124</sup>I-iothalamate) per minute, its functionality is related with nephron numbers [10,11]. GRF easily identified chronic kidney disease, which is less than 60 mL/min, 1.73 m<sup>2</sup>, and lengthy 3 months period [7]. We can also based on chronic kidney disease with five stages via GFR levels [12], first stage diagnostic stage (GFR ≥ 90), second stage progressive (GFR 89-90), third stage complication treatments (GFR 30-59), fourth stage kidney replacement stage (GFR 15-29) and last stage GFR < 15 dialysis or kidney transplant [13].

### Some biomarkers of kidney disease

Herein some useful biomarkers for evaluating kidney disease;

**Beta-Trace Protein (BTP):** Beta-trace protein is known as prostaglandin D synthase, small weight (23-26 kDa) and filtered by kidneys [14,15]. It is synthesized all tissues except ovary cells and responsible for maintaining plate aggregation inhibition, vasodilation [15]. The relationship between GFR and BTP was investigated by Donadio, C. et al., that result presented the negative correlation between GFR and BTP ratio during kidney failure. Another study based on 115 diabetic patients with type I and type II [16], then evaluated BTP quantity with polyclonal (rabbit) assay and as a consequence of their results supported that BTP may be useful for diagnostic of GFR. In last study was based on isolation of BTP from different body fluids (healthy and renal disease patients) and evaluated Western blot analysis after immunoaffinity chromatography [17]. According to study results, renal patients BTP values were found higher than healthy people and may be used as a biomarker for kidney disease.

**Kidney Injury Molecule 1 (KIM-1):** Kidney injury molecule-1 is one of the Q glycosylated trans membrane protein (type 1 mucin), has six cysteine in outer domain like an immunoglobulin and also

plenty of some amino acids threonine, serine and proline in two- N glycosylation region [18]. Normally KIM-1 is synthesized lower quantities by kidneys, but during post-ischemia, KIM-1 level gets higher [19]. The expression rate of KIM-1 occurred tubular epithelial cell damage [18], according to in situ hybridization with immune-histochemical studies showed that expression rates of KIM-1 and mRNA get higher during regeneration period of tubular epithelial cells [19]. According to some literature studies; Han, K.W. et al., acclaimed that patients with kidney failure's urea (post-ischemia), KIM-1 quantities were higher than healthy people checked with ELISA and Western blot analyses [20]. Another study was related with allograft patients (including diabetes patients) urea, evaluated with KIM-1 kit and KIM-1 ratio were found higher owing to renal dysfunction [21].

**Interleukin-18 (I-18):** Interleukin-18 is member of I-1 cytokine super family, synthesized by active macrophage and expressed high levels during I-18 chronic inflammation, autoimmune disease, various cancer species and some infections [22,23]. In literature studies, positive correlation between I-18 levels and kidney damage occurred. For example Parikh, R.C. et al., [24], compared with I-18 levels between healthy people to AKI patients for use ability of I-18 as a proximal tubular injury biomarker. Research results; I-18 may be used an alternative biomarker for kidney injury. Another study was represented from intensive care unit patients with acute lung injury and AKI; checked urea levels both of them [25]. According to 24 and 48 hours urea results, supported that I-18 could be used an early AKI diagnostic marker.

**Albuminuria (AL):** Albumin contains 585 amino, 66 kDa, negative charge protein known as microalbumin (30 mg < X < 300 mg) in urea which used an ideal marker for determining protein levels with creatinine [26,27]. Albumin filtered by two steps firstly by glomerulus then reabsorbed by proximal tubular cell, with respect to cubilin with megalin receptors transport albumin into lysosomes for endocytosis [28,29]. High urea protein (albumin/micro albumin) levels used an independent risk factor not only kidney damage but also cardiovascular disease [30], pointed out correlation between proteinuria to kidney

damage. Another research study results also (602 CKD patients high AL level) supported the positive correlation between kidney damage and albuminuria [31]. The last proteinuria study was based on kidney damage-progression periods via myocardial infarct and high proteinuria levels were found both of them [32].

#### **Neutrophil Gelatinase-Associated Lipocalin**

**(NGAL):** NGAL covalently binds gelatinase, (localized in neutrophil) which has 178 amino acids and 25 kDa molecular weight [33, 34]. It is easily detected in urine samples and high resistance for degradation wherefore small molecular weight [35]. Besides AKI was used also diagnostic, progression of CKD [36]. First research article was based on comparison NGAL ratios (Elisa kit) between 96 renal disease patients to 14 normal patients [37]. 96 patients were divided in 2 groups; (progressive renal patients and non-progressive renal patients) and 2 results were given by researchers, firstly; serum and urine NGAL values were detected higher (renal failure patients and progressive renal disease patients) than healthy with non-progressive patients secondly NGAL might be useful biomarker for checking CKD progression [37]. Second study was related about 71 children NGAL urine samples and blood levels after cardiac surgery versus healthy volunteers (adult) [38]. This study validation was checked with Elisa kit (quantitation), Western blot (expression-quantitation). NGAL levels were not detected healthy volunteers (10 people) and children who (any cardiac operation) urine samples but NGAL levels were detected acute renal injury patients so NGAL might be increased during acute renal injury especially after cardiac operation by authors.

#### **Asymmetric Dimethylarginine (AD):**

Asymmetric dimethylarginine was firstly diagnosed hemodialysis patients, molecular weight 220-dalton and endogen inhibitor of nitric acid oxidase [39,40,41]. It is occurred with methylation after proteins posttranslational (especially arginine) with respect to residues of some proteolytic enzymes [41,42]. Two literature studies were given for AD; first one given by Fliser, D, et al., [43] compared with AD ratio level towards GFR ratio. In normal GFR ratio, AD levels

could be the normal and a tolerated level whereas kidney damage patient's ratios get higher level [44]. Second study was related high AD serum levels of CRF patients, reduced lower AD serum levels after dialysis and pointed out by authors [44].

#### **Urinary N-Acetyl- $\beta$ -D-Glucosaminidase (NAG):**

NAG is approximately 140 kDa molecular weight, located in the proximal tubule cells synthesized by lysosomes that has 2 different isozyme forms NAG A, NAG B [45,46]. Because of high molecule weight, not easily filtered by kidneys, high levels of NAG were an indicator of lysosomal and inside proximal tubular damages in urine samples [46]. Some literature studies supported this idea, such as Liangos, O. et al, [47] examined 201 AKI patient's NAG and KIM-1 levels for 3 years, checked NAG enzyme activity with spectrophotometer method referred that NAG with KIM-1 might be used a biomarker for AKI. Another literature study was evaluated creatinine and NAG enzyme activity urine samples 1<sup>st</sup> day, 3<sup>rd</sup> day (after transplantation) and 12<sup>th</sup> months levels of 87 kidney transplantation patient as a consequence, NAG may be used an ideal biomarker of early tubular damage activity and long term kidney transplantation [48].

**Cystatin C:** Human cystatin C is an endogenous biomarker for AKI with CKD, nearly 13.6 Da molecular weight, 120 amino acids residues, 151 nm diameters that is filtered and catabolized respectively by glomerulus and kidneys [49,50,22]. In serum plasma its level is 0.8-1.2 mg/mL [49]. First literature study, which was related to comparison between renal disease patients (115 patients) and healthy people (121 people) owing to serum cystatin C/creatinine levels [51]. As a result, serum cystatin C might be a useful biomarker than creatinine for renal disease by authors. Second study; 418 healthy person and 37 patients with CKD (including type 2 diabetes) were selected for analyzing serum/plasma cystatin C and creatinine ratio during GFR levels [52]. According to study results; cystatin C which could be useful early diagnostic biomarker for CKD, positive correlation ratio between type 2 diabetes patients and good alternative for evaluating CKD stages especially stage 2.

#### **Liver Type Fatty Acid-Binding Protein**

**(L-FABP):** FABPS protein family is 15 kDa molecular weight, found in mammalian and rodents tissues, which is responsible for carrying long fatty acids [53]. L-FABP (14.4 kDa) expressed human proximal tubular cells and necessary for -oxidation [54]. First study based on renal disease patients, according to experimental results positive correlation between L-FABP to tubular damages and urine kidney damage proteins were reported [55]. Second study was based on 120 nondiabetic chronic renal patients divided into 3 groups via proteinuria levels then compared with L-FABP levels [54]. L-FABP levels were found especially higher heavy proteinuria group than other groups (mild and moderate proteinuria), according to researchers; L-FABS could be useful identification biomarker for renal diseases.

#### **CONCLUSION**

Herein, some specific biomarkers were given and supported by research articles for detecting kidney disease. In this review; some biomarkers compared with each other's for evaluating renal disease, beside some biomarkers were also used for detecting not only kidney disease but also another health problems. As a result; for diagnosis, treatments, progression of diseases control and prolonged life, biomarkers are always indispensable molecules for our life.

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