New biomarkers for diagnosing and treatment of kidney failure disease

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Abstract

Start losing its ability to filter nitrogenous waste product from the blood, leading to its retention. kidney failure has become one of the most common diseases in this century. It occurs when the kidneys are harmed. Reduced urine production, swelling of the legs, ankles, and feet, shortness of breath, exhaustion, nausea, confusion, seizures, chest pain, and coma are all indications of renal failure. There are two types of kidney disease: acute renal injury and chronic renal failure. Acute kidney damage is characterized by a reduction in glomerular filtration rate that lasts from hours to days and is usually reversible. For chronic renal disease, which is usually irreversible and is defined by a decline in glomerular filtration rate to less than 60 ml/minute or increased serum creatinine for more than 3 months .Cr, BUN, Alb, UA and Urea, are one of the classic biomarkers that have been used for many years to predict the renal failure, but because they display poor specificity and sensitivity in predicting early changes in kidney function, therefore there were a need for new biomarkers that give more accurate and specific results than the classic biomarkers. The new biomarkers include, kidney injury molecule1 (KIM1), neutrophil gelatinase associated lipocalin (NGAL), cystatin-C (cyc-C), clusterin (clu), interleukin-18 (IL-18), alpha-1 microglobulin (a1 M), beta-2 microglobulin (b-2 M), osteopontin, asymmetric dimethylarginine (ADMA), inducible nitric oxide synthase (iNos), livertype fatty acid binding protein (L-FABP), and Fetuin-A. Therefore the study aims to shed light on the most important of these evidence.

Keywords: Renal failure ,classic biomarkers , new biomarkers.

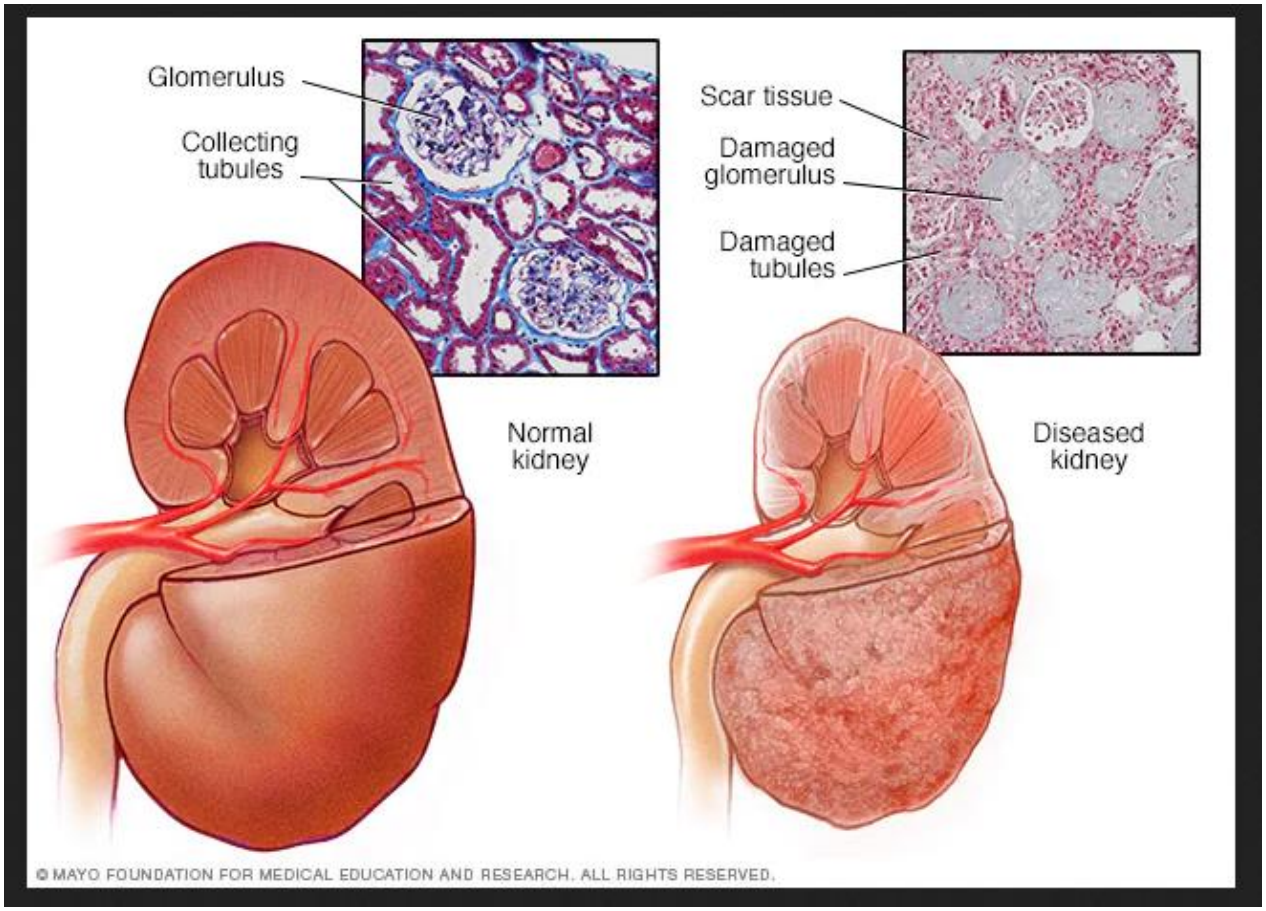
الخلاصة:

تظهر اعراض الفشل الكلوي عندما تبدأ الكلية في فقدان قدرتها على تصفية منتج النفايات النيتروجينية من الدم ، مما يؤدي إلى احتباسها. أصبح الفشل الكلوي أحد أكثر الأمراض شيوعًا في هذا القرن. يحدث ذلك عندما تتلف الكلى. تشمل أعراض الفشل الكلوي انخفاض كمية البول وتورم الساقين والكاحلين والقدمين وضيق التنفس والإرهاق والغثيان والارتباك والنوبات وألم الصدر والغيبوبة. وهي مقسمة إلى نوعين: إصابة الكلى الحادة وأمراض الكلى المزمنة. تتميز إصابة الكلى الحادة بانخفاض معدل الترشيح الكبيبي الذي يستمر من ساعات إلى أيام وعادة ما يكون قابلاً للعكس. لأمراض الكلى المزمنة ، والتي عادة ما تكون غير قابلة للشفاء وتتميز بانخفاض معدل الترشيح الكبيبي إلى أقل من 60 مل / دقيقة أو ارتفاع الكرياتينين في الدم لأكثر من 3 أشهر. واحدة من المؤشرات الحيوية الكلاسيكية التي تم استخدامها لسنوات عديدة للتنبؤ بالفشل الكلوي ، ولكن لأنها تظهر ضعف الخصوصية والحساسية في التنبؤ بالتغيرات المبكرة في وظائف الكلى ، لذلك كانت هناك حاجة إلى مؤشرات حيوية جديدة تعطي نتائج أكثر دقة ومحددة من المؤشرات الحيوية الكلاسيكية. تشمل المؤشرات الحيوية الجديدة ، جزيء إصابة الكلى 1 ((KIM1، العدلات الجيلاتينية المرتبطة ليبوكولين ((NGAL، سيستاتين- C (cyc-C)، clu ، انترلوكين 18 ((IL-18، alpha-1 ميكروغلوبولين ((a1 M، بيتا 2 ميكروغلوبولين (b- 2 M)، osteopontin ، ثنائي ميثيل أرجينين غير متماثل ((ADMA، سينثيز أكسيد النيتريك المحرض ((iNos، بروتين رابط الأحماض الدهنية من النوع الحي ((L-FABP، و .Fetuin-Aلذلك تهدف الدراسة إلى إلقاء الضوء على أهم هذه المؤشرات.

1-Introduction

1.1 Renal failure

Renal failure is defined as the kidneys' inability to conduct excretory activities, which results in the accumulation of nitrogenous wastes in the bloodstream. The kidney performs the following functions: Volume and electrolyte regulation Nitrogenous waste excretion Many drugs, for example, are eliminated through the elimination of exogenous molecules. A variety of hormones, such as erythropoietin, are synthesized. Insulin, for example, is metabolized by low molecular weight proteins. The two types of kidney failure are acute renal failure and chronic renal failure. [1]. Low urine production, swelling of the legs, ankles, and feet due to fluid retention brought on by inability of kidneys to eliminate water waste, unexplained shortness of breath or exhaustion, persistent nausea and/or pressure in the legs, and/or drowsiness are all possible symptoms.. [2].



Figure(1-1) Normal kidney and Kidney injury

1.1.1 Acute kidney disease

Acute kidney disease (AKD), also referred as acute kidney failure (AKF), is a sickness defined by a reduction in renal function as a result of complicated pathophysiological causes. AKD is the most prevalent cause of hospitalization and is related both with short - range and long mortality and morbidity. This can lead to heart disease and contribute to the progression of chronic kidney disease (CKD)[3]. Acute kidney disease (AKD) is defined by the sudden and often reversible loss of kidney function that develops over days or hours and resulting in the accumulation of nitrogenous as well as other waste material normally removed by kidneys. It is based on serum urine and creatinine output. [4] Acute kidney failure(AKF) pathophysiology is divided into three subgroups:

1-prerenal 2-renal 3-postrenal

1-Prerenal is a type of acute kidney injury caused by a decrease in blood flow to the kidney. This is a type of systemic hypoperfusion caused by hypotension or hypovolemia, or by selective kidney hypoperfusion produced by kidney aortic stenosis and dissection.

2-Renal occur in sepsis-induced acute tubular necrosis and renal ischemia [mean arterial pressure less than 70mmHg].

3-Postrenal nephropathy is a type of obstructive nephropathy caused by mechanical urine flow obstruction induced by renal stones, tumors, prostatic enlargement, and congenital problems

Postrenal causes a reduction in glomerular filtration rate (GFR)[5]. Risk factors for acute kidney disease include arterial hypertension, chronic vascular disease, diabetes, and cardiac failure. Acute kidney injury has an impact on tubular function in both the proximal and distal tubules [6].

AKD is linked to heart, brain, lung, and liver disease in distant organs. One of the most common complications in patients have acute kidney injury is acute lung injury. Cardiovascular toxicity is caused by an elevation in the heart muscle ischemia due to a decrease in coronary vasoreactivity due to the accumulation of uremic toxins. Acidosis and alveolar edema in acute renal illness patients are caused by fluid overload and hyperventilation as a result of depression in heart output and urine production, which is the primary cause of lung dysfunction in these patients. [7].

1.2.2 Chronic kidney disease:

An individual's health is adversely affected by chronic kidney disease (CKD), which is defined by long-term structural or functional abnormalities in the kidneys. Imaging can reveal structural abnormalities such as cysts, tumors, malformations and atrophy. Hypertension, oedema, and kidney failure are all symptoms of kidney disease. Growth retardation in children, and changes in urine production or quality; these changes are most typically identified by the elevation of creatinine levels in the serum, cystatin-C, or the levels of urea nitrogen in the blood. The most common pathological symptom of CKD is renal fibrosis., regardless of the underlying injury or disease. People over the age of 65 are more likely to develop CKD (all stages), but the risk of progressing to end-stage renal disease. (ESRD) is more common in those under the age of 65 who have kidney disease. In spite of the fact that women are more likely to have CKD than men, men are more likely to advance to ESRD than women.[8]

1.2 Biomarkers

Biomarkers (short for biological markers) are considered biological indicators of a person's health. "A trait that is scientifically analysed and assessed as an indication of natural biological systems, pathologic, or pharmacological responses to a medical approaches," according to the concept of a biomarker.[9]

1.2.1 Classic biomarkers

1.2.1.1 “Blood Urea Nitrogen”(BUN)

“Blood urea nitrogen” is one of the medical tests used to diagnose kidney disease. The normal of increased urea nitrogen are ingestion of food with a high nitrogen content, glomerular filtration rate, hypovolemic shock, heart failure,

gastrointestinal hemorrhage, fever, and increased catabolism. Urea-derived nitrogen in the bloodstream (a substance formed by the breakdown of protein in the liver). Urea is removed from the bloodstream and excreted in the urine by the kidneys. A high urea nitrogen content in the blood could indicate a kidney issue. Also known as BUN or urea nitrogen. BUN is more sensitive for patients have renal failure and cardiovascular disease, it has been prognostic in other many conditions like acute pancreatitis, acute pneumonia and acute intracerebral hemorrhage, The rate of blood urea nitrogen was 15.1 mg/dl. The degree of baseline comorbidity, as well as unfavorable presenting characteristics, increased in a stepwise manner. Blood urea nitrogen and cardiovascular outcomes: High BUN levels were linked to an increase in death at thirty days and during the period of the study. Patients who have greater blood urea nitrogen were more likely to develop recurrent myocardial infarction and congestive heart failure by thirty days. They were less likely to have revascularization, had a higher risk of stroke, and had more adjudicated bleeding events. When there is ST _segment deviation; cardiac marker elevation, such as baseline troponin, Troponin (I or T)—is protein normal value (0 4 mg /ml), this is protein the most usually ordered and most specific of the cardiac markers. Within a few hours of cardiac injury, it is raised (positive) and. Rising troponin levels in a number of troponin tests over several hours can aid in the diagnosis of a heart attack[10]. BUN inhibits both macrophage proliferation and the synthesis of nitric oxide: Because decreased nitric oxide synthesis has been linked to atherosclerosis progression, we looked into the relationship between urea inhibition of (iNOS), macrophage proliferation as measured by cell counting, tritiated thymidine incorporation, and cell protein measurement, and macrophage apoptosis as a marker of regulated rennin angiotensin system. [11]

1.2.1.2 Creatinine(Cr)

Creatinine is a non-enzymatic metabolic product of creatinine and phosphocreatine, which is normally produced at a constant rate from skeletal muscle tissue (about 2% per day of total creatinine pool) It is not reabsorbed, but is secreted by the proximal tubule in a variable percentage, which increases as renal failure progresses.[12] Normal reference intervals "0.63-1.16 mg/dL" for (white) men and "0.48-0.93 mg/dL" for (white) women between the ages of 20 and 70 are maintained for the typical healthy subject, with SCr being stable for the average healthy subject between twenty and seventy years of age. [13]. In patients with moderate to severe "Acute Kidney Injury" (AKI stage 2 and 3), the serum creatinine rate rose in the first 8 to 16 hours, but only marginally in patients with mild AKI (stage 1). Additionally, it was found to be normal in patients with no history of "acute kidney injury (AKI)". The first 24-hour peak sCr value was revealed to be the strongest predictor of moderate to severe AKI as opposed to mild "AKI/No AKI". [14]. In another study, it was discovered that increased sCr levels at T0,T1 and T2 (T0: post-natal day1, T1: post-natal day3, T2: post-natal day7) were associated with gestational age (GA), patent ductus arteriosus (PDA) and, antenatal maternal hypertension (MH). For this

reason, in compared with modified kidney biomarkers, sCr is only sensitive to detect minor degrees of kidney injury [15].

1.2.1.3 Uric acid(UA)

Uric acid is a heterogeneous cyclic compound, a natural compound in the body consisting of carbon, oxygen, nitrogen and hydrogen, and it is the final product of the metabolism of purines in the human body. Purines are natural compounds found in foods in varying proportions. Chemically it is the compound C5H4N4O3. Blood contains uric acid, which is a waste product. Uric acid levels in the blood should be kept at the following levels: 4.0-8.5 mg/dL in adult males. Female adult: 2.77.3 mg/dL The majority of uric acid can be dissolves in the bloodstream, travels through the kidneys, and eliminated from the body through urine. However, when the kidneys do not effectively eliminate uric acid, a high uric acid level develops. Uric acid can pile up and produce urate crystals as blood is passed via the kidneys. Urate crystals can harm and scar the kidneys as they pass through. If gout is not treated, this kidney damage is thought to progress to renal disease and failure over time [16].

1.2.2 New biomarkers

1.2.2.1 "Beta-2microglobulin(B2M)"

All cells in the body secrete "beta-2microglobulin(B2M)", a protein that may be detected on the surface of nearly every cell. It is found in most bodily fluids, and its concentration rises when there is an increase in cell creation and/or destruction or an increase in the immune system. B2M can be discovered in the blood, urine, or "CSF" using this test. The beta-2 microglobulin(B2M) blood test is used to detect kidney damage and to monitor kidney disorders. Because of its mini size, it can be filtered directly at the glomerulus and decomposed by the kidney's proximal tubular cells.[17].

Urine "beta2-microglobulin" as a possible marker for chronic tubular dysfunction A high level of "beta-2-microglobulin" in the urine suggested nephrotoxins and reduced the glomerular filtration rate (GFR) and creatinine between two weeks and three months. Beta-2microglobulin concentration in urine could correlate well with kidney injury molecule on kidney biopsy and can accurately predict acute kidney injury “AKI” in sepsis patients. Tubulointerstitial nephritis is a good diagnosis by “beta-2-microglobulin”. “Beta-2-microglobulin” is filtered by glomerular structure alterations from different glomerular diseases causes increased glomerular permeability and overflow proteinuria. During the healing phase of nephrotoxic acute kidney injury, the concentration of beta-2-microglobulin in urine rises. Beta-2-microglobulin excretion in urine indicates incomplete renal tubular healing following acute kidney injury “AKI” . Beta-2-microgloulin as mediator and marker of some of the complication of uremic syndrome [18].

1.2.2.2 Alpha-1 microglobulin(a-1M)

Alpha-1-microglubulin(a-1 M) is also called protein [HC], is small protein found in all vertebrates including humans, and it's distributed in extravascular tissue and blood plasma of all organs. It's used for protection of cells and tissues and the glomerulus removes it and the proximal tubules reabsorb it. a-1-M has been properties as therapeutic agent and renal antioxidant . Early identification of nephropathy in diabetes can be improved by detecting elevated levels of A1M in the urine, particularly in the proximal tubules. It was also claimed that urine A1M could serve as a cheap and non-invasive diagnostic tool for tubular diseases. [20]. Alpha-1-microglobulin as indicated of acute or chronic kidney disease , alpha-1-microglobulin has potent antioxidant activities and has ability to bind pro-oxidant free heme with tissues or circulation , alpha-1-microglobulin has been bind to immunomodulatory cells (T and B cells, polymorphonuclear cells and natural killer cells) and potentially inhibit pro- inflammatory effect. a-1-M has protective role in both organs damage and effects as elevated blood pressure in preeclampsia ; has pathological condition associated with oxidative stress[20].

1.2.2.3 Nitric oxide synthase inducible(iNOS)

The enzyme “inducible nitric oxide synthase (iNOS)” is essential for the formation of nitric oxide (NO) from L-arginine.. Nitric oxide (NO) is a molecular signaling molecule that is important in cellular signaling. It aids in the modulation of vascular tone, airway tone, insulin secretion, and peristalsis. iNOS regulates kidney function. Nitric oxide (NO) plays numerous roles in the kidney, including controlling renal haemodynamics, sustaining medullary perfusion, mediating pressure-natriuretic response , blunting tubuloglomerular feedback, inhibiting tubular sodium reabsorption, and modulating renal sympathetic neural activity. Long-term blood pressure control and up-regulation during inflammatory conditions in renal epithelial cells **[21].** Nitric oxide produced in tubular cells by inducible nitric oxide synthase (iNOS) can increase oxidative damage, resulting in tubular damage. Inhibiting inducible nitric oxide synthase (iNOS) improved tubular function by suppressing oxidative stress production and proteinuria. Nitric oxide production is reduced in chronic kidney disease (CKD**)[22].**

1.2.2.4 Asymmetric DimethylArginine “ADMA”

Protein methylation, a typical method of post-translational protein modification, produces “asymmetric dimethylarginine (ADMA)”. It’s normal value 0.4-1 uM/L . It is the most potent endogenous nitric oxide synthase (NOS) inhibitor, and large levels of asymmetric dimethylarginine are found in patients with “end-stage renal disease” (ESRD). Asmmetric dimethylarginnes must be related to adverse cardiovascular events and mortality in dialysis patients. [23].Kidneys have dual function in metabolism of asymmetric dimethylarginnes ; they excrete ADMA and high level of dimethylarginine dimethylaminohydrolase [DDAH is important enzyme

of regulates of ADMA levels in tissues and intracellular and it hydrolysis of ADMA to Lcitrulline and dimethylamine].ADMA is considered as uremic toxin , the circulation of ADMA concentration decrease slowly and moderately during dialysis. the concentration of ADMA is increasing again and reach high level compared to the baseline. An increase in ADMA was linked to a decrease in "glomerular filtration rate" (GFR). Patients with chronic kidney disease have an increased risk of cardiovascular morbidity and mortality. Increase high level of ADMA is associated with more rapid renal diseases progression and mortality. [24].

1.2.2.5 "Cystatin-C"

"Cystatin-C (Cys-C)" is a 13-kDa non-glycosylated protein that belongs to the cysteine protease inhibitor superfamily[25]. "Cystatin C" is synthesized continuously by nucleated cells and is present in relatively high amounts in a variety of physiological fluids, most notably seminal fluid, cerebral fluid, and synovial fluid. Normal serum cystatin C concentrations vary between 0.6 and 1 mg/l[26]. The glomerular cells filter it, and it is nearly completely reabsorbed and easily degraded (but not secreted) in the proximal tubule. Urinary CyC outperformed SCr and plasma CyC in detecting acute renal damage in the early stages[28]. Cystatin levels in the serum are not related to gender, muscle mass, or age. Numerous research have been undertaken to determine the value of serum Cys-C as a proxy for GFR or as a biomarker. In one study, serum Cys-C was found to be a helpful biomarker of acute renal failure, as it could be detected one to two days before blood creatinine levels increased (SC). Although blood Cys-C levels were discovered earlier than SC levels, they were not predictive of renal illness and, like SC, indicated kidney injury long after significant damage had occurred..[26].

1.2.2.6 Osteopontine

Osteopontine is acidic glycoprotein , it has been found intracellular and extracellular tissue as well as soluble cytokine in plasma and urine. Expressed in various cell types of body including brain, bone, endothelial cell, immune and smooth muscle , it appears in the both acute and chronic kidney injury. Its normal value 31-200 ng/ml. Osteopontine is pro- and Anti- inflammatory molecule simultaneously attenuates oxidative stress. Both oxidative stress and inflammation have various physiological and pathophysiological of glomerulonephritis and in the progression of kidney damage.Osteopontine has important role for interplay between the cardiovascular system and kidney. It has been linked to the formation of atherosclerotic plaques by increasing local levels in vessel walls. Multivariable logistic regression models of the associated between osteopontin and incidence of "chronic kidney disease, glomerular filtration rate (GFR)<60ml/min". High urinary osteopontin was significantly linked to chronic kidney disease in kidney function. Urinary osteopontin linked to "glomerular filtration rate" (GFR) decline in models .Secondary analyses associated with and without prevalent cardiovascular disease. Plasma osteopontin associated with risk of cardiovascular death [27].

1.2.2.7 "Neutrophil gelatinase associated lipocalin (NGAL)"

NGAL is a 25-kDa lipocalin family protein that is also known as siderocalin, lipocalin 2, or oncogene 24p. Additionally, Low quantities of NGAL are found in a range of cell types, such as the salivary gland, uterus, prostate, trachea, lung, stomach, colon, and kidney. Its production increases with age and is significantly more in females than in males[28]. The primary sources of NGAL in the body are leucocytes, the loop of Henle, and collecting ducts. Tubular epithelial cells express it in response to injury and tubulointerstitial damage, which typically occur throughout the progression of kidney disease[29]. Females had a median random urine NGAL concentration of "27.0 ng/mL (range 0.2–153.9 ng/mL)" compared to males who had a median of "12.5 ng/mL (range 0.0–40.8 ng/mL)"[30]. While NGAL levels in healthy people' plasma range between "28.7 and 167.0 ng/mL"[31]. According to clinical report, the urine biomarker NGAL was abnormal on admission in all instances with AKI, subsequently increased and peaked between 4 and 8 hours. Between 16 and 24 hours later, it returned to normal. uNGAL was found to be a more sensitive diagnostic biomarker for acute kidney injury stages 2 and 3 (AKI2/3) than serum creatinine after 4 to 8 hours. High levels of NGAL in blood and urine were associated with the development of kidney disease in a variety of nephropathies, such as diabetic nephropathy, lupus nephritis, polycystic kidney disease, and IgA nephropathy. Both serum and urine NGAL indicators were effective in predicting the development of renal impairment after a median follow-up of 18.5 months. Additionally, it was revealed that every "300 ng/ml" increase in urine NGAL was linked to elevate the risk of progressing chronic kidney disease (CKD), end stage kidney disease (ESKD), or mortality in non-dialysis CKD patients, as well as an increased risk of death in dialysis patients. That is why the NGAL biomarker is one of the most predictive biomarkers for AKI and CKD progression, particularly in the late stages. [31].

1.2.2.8 "Kidney injury molecule-1"

"Kidney injury molecule-1 (KIM-1)" is a type I glycoprotein found on the surface of cells (104 kDa). Additionally, "KIM-1" is a phosphatidylserine receptor located on renal epithelial cells that identifies and facilitates the phagocytosis of apoptotic cells[32]. KIM-1 concentrations in healthy human urine and serum are less than 1 ng/ml. Meanwhile, it may be raised to 3-7 ng/ml following ischemic kidney damage. [33]. It has been most widely investigated for both AKI and CKD proximal tube injury[32]. In comparison with "non-acute kidney injury (non-AKI)", urinary KIM1 level was significantly elevated in AKI diagnosis after 2 and 6h, but its sensitivity decreased to 74 per cent after 12h. The level of urinary KIM-1 was substantially high. Multiple factors such as sepsis and the use of contrast media affect the urinary concentration of KIM-1. Common diseases such as atherosclerosis, diabetes mellitus and high blood pressure may also be affected. In this study, a sensitivity of 48% and a specificity of 94% were observed at 1,9ng/mL after 3 hour of urinary KIM-1[34].

1.2.2.9 "Liver-type fatty acid binding protein (L-FABP)"

Liver-type fatty acid binding protein (L-FABP) is a 14-kDa endogenous antioxidant protein from the lipid-binding protein superfamily that is predominantly produced in the liver. LFABP is located in the proximal tubule of the kidney and is released into the tubular lumen together with other toxic peroxisomal products. It has a typical range of "0.12 to 20.09 ng/ml", with a mean of "1.60 ng/ml"[35]. Urinary L-FABP levels in the acute kidney injury (AKI) group were significantly higher than those in the non-AKI group at baseline, 24 hours later, and 48 hours later. At 48 hours, urinary L-FABP levels were lower in the AKI group but not in the non-AKI group. According to multivariate regression analysis, the level of LFABP in the urine was the only independent predictor of AKI at baseline. Furthermore, the baseline urine L-FABP level was significantly higher in patients with contrast-induced acute kidney damage (CI-AKI) than in those with non-contrast-induced AKI, indicating that this is a predictive marker for CI-AKI in patients with moderate chronic kidney disease. Urine LFABP is a sensitive indicator of AKI in people who have had an abdominal aortic aneurysm repaired, and urinary LFABP levels before surgery can predict the development of AKI after surgery, especially in people who have had endovascular aneurysm repair. [36].

1.2.2.10 Clusterin(Clu)

Clusterin(Clu) is normal value 22-88 ug/ ml. In all cases of "acute kidney injury (AKI 1 and AKI 2/3)", the urinary clusterin biomarker was elevated and peaked within the first 4 hours, relative to patients without AKI. For mild AKI (AKI 1), uClu concentration fell into the normal range after 4 to 8 hours, However, for moderate and severe AKI, it remained greater and erratic. (2/3). Between 8 and 16 hours, it dropped to within the usual range for moderate/severe AKI. From 4 to 8 hours, the three novel biomarkers "urinary clusterin, urinary neutrophil gelatinase associated lipocalin, and serum Cystatin-C (uClu, uNGAL, and sCysC)" appeared to be more accurate diagnostic biomarkers of AKI 2/3 than serum creatinine(sCr). Clusterin levels in rats' kidneys increased after "ischemia reperfusion injury, toxicant-indued kidney injury, and unilateral urethral obstructions", suggesting that clusterin could be the first sign of AKI[15]. Levels of urinary clusterin increased nearly threefold after 24 hours in another clinical trial, then plateaued after 14 days, before increasing again in the third week. (37)

1.2.2.11 Interleukin-18 (IL-18)

Interleukin-18 (IL-18) is a protein that has a role in ischemia acute tubular necrosis. Its normal concentration is 460 pg/ml. Although it has been shown to be a quick, reliable, and low-cost test marker for the early diagnosis of acute kidney injury (AKI), its prediction accuracy varies significantly.. We analyzed data from 2,796 individuals in 11 studies conducted in three countries. These studies had limitations on the variability of threshold and nonthreshold impact. The diagnostic odd ratio (OR) for urine IL18 level to predict AKI was "5.11 [95 percent confidence interval [CI] 3.22–8.12]", with a sensitivity and specificity of "0.51 and 0.79", respectively. The area under the receiver operating characteristic curve for predicting AKI using urine IL-18 levels was "0.77 (95 percent confidence interval [CI] 0.71–0.83)".

Subgroup analysis found that urine IL-18 levels in pediatric patients (18 years) and early AKI prediction time (12 h) were more predictive of AKI, with diagnostic odds ratios of "7.51 (2.99–18.88) and 8.18 (2.19–30.51", respectively. The difficulty with IL-18 as a substance, Patients with acute tubular necrosis have considerably higher urine IL-18 levels than stable controls and patients with a range of different renal illnesses, including urinary tract infection, chronic renal insufficiency, and pre-renal azotemia, according to cross-sectional studies. As a result, the pathophysiology of IL-18 remains unknown, as does its true function as a mediator of certain forms of damage rather than a marker of harm. While AKI can result in the production of IL-18 in the proximal tubule and its subsequent release into the urine via caspase-1 cleavage, it can also result from lung injury or heart ischemia. [38]

1.2.2.12 "Fetuin-A"

"Fetuin-A" is a negative acute-phase response protein that is generated in the liver and secreted into the bloodstream, where it inhibits the release of tumor necrosis factor-alpha stimulated by lipopolysaccharide in vitro and in vivo. Its normal concentration is 140-300 ng/ml. The concentration of serum has decreased. Fetuin-A cocentrations are linked to a greater mortality rate in dialysis patients and can predict mortality in chronic renal disease patients. Exosomal Fetuin-A can be produced by the kidney, but it can also be discovered in the urine as a result of insufficient proximal tubule processing in proteinuria conditions (a type of overflow protein urea) or tubular cell apoptosis. FetuinA was discovered in apoptotic vascular smooth muscle cells and apoptotic cells were observed in tubular cells in rats with cisplatin- or ischemia and reperfusion (I/R)-induced acute kidney damage (AKI). [39]

2.conclusion:

•Kidney failure is a common complication that carries a high morbidity and mortality rate.

Nephrotoxicity is responsible for the high occurrence and distribution of KI in both hospitalized and non-hospitalized persons.

• The most sensitive and specific KI biomarkers are "urinary clusterin, IL-18, KIM-1, and NGAL, and great progress has been made in creating high-throughput quantitative technology for their assessment. More multicenter and long-term trials are needed to speed up bench-to-bedside translation".

• Numerous challenges must be solved in biomarker discovery, evaluation, and validation, such as "standardization of biospecimen collection, handling, and storage processes; biomarker normalization; and reference range construction".

•Individual KI biomarkers and panels will be identified and validated, providing the early identification of kidney injury, enhanced prediction and outcomes, and distinct patient classification methods for interventional trials.

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