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CHANGES IN CLINICAL-LABORATORY PARAMETERS IN KIDNEY DYSFUNCTION ACCORDING TO THE DEGREE OF IMPAIRMENT OF PATIENTS AT RISK [8]

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Abstract: *A number of chronic, systemic diseases lead to kidney damage without being primarily renal. Renal diseases do not have specific symptomatology and are most often detected at an advanced stage. Three of the most common causes of chronic kidney disease are diabetic nephropathy, hypertension and diabetes.*

A biomarker is defined as an objectively measured characteristic assessed as an indicator of normal biological processes, pathological processes, or response to pharmacological response to therapeutic interventions. For acute or chronic kidney disease, biomarkers must show rapid and reliable changes with disease progression, be specific, sensitive, rapid, and indicate damage to different segments of the nephron.

In this article, we review conventional biomarkers - clinical and laboratory tests such as serum creatinine, proteinuria, glomerular filtration rate, and others - as a tool for early recognition of acute and chronic kidney injury, differential diagnosis, prognosis assessment, treatment response, and functional recovery, divided into four main groups: basic assays, advanced assays, specialized assays and special low molecular weight proteins related to changes in the basic functions of the kidney and the physiological processes occurring in the kidney - filtration, resorption and secretion.

Keywords: *Kidney damage, Kidney dysfunction, Biomarkers*

INTRODUCTION

Rapidly progressive kidney failure is the initial clinical diagnosis in patients with progressive renal impairment of short duration. (Bhowmik, D. et al. 2011).

Chronic kidney disease - these are diseases that can be considered in stages, which are characterized by the fact that the kidneys do not cope well enough with their usual functions. In the later stages, these diseases can develop into kidney failure. Often this type of disease is a secondary disease due to other diseases such as diabetes or hypertension.

Due to the use of different definitions of acute renal failure in the literature, a panel of experts from the Acute Dialysis Quality Initiative classified patients with renal dysfunction according to the degree of impairment into: patients at risk, with impairment, with reduced function, with prolonged loss of renal function, and end-stage renal impairment. This classification is intended to assess the

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epidemiology and predict the outcome of ESRD. Renal dysfunction is no longer considered significant only when it reaches the stage of failure, but also early risk. Relatively mild dysfunction is also associated with adverse outcomes (Kellum JA et al., 2007).

Although numerous articles have been published in the literature on the use of novel urinary and serum biomarkers for the diagnosis and prognosis of UC, there is still no reliable tool to distinguish between true parenchymal and prerenal azotemia. The biomarkers studied for association with acute kidney injury are - neutrophil gelatinase associated lipocalin (NGAL), kidney injury molecule -1(KIM -1), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-18 (IL-18), N-acetyl-glucosaminidase (NAG), glutathione transferase (GST), liver fatty acid binding protein (LFABS) - measured in serum, plasma or urine. Biomarkers reflect the overall severity of disease but are not specific for kidney damage (Vanmassenhove J et al., 2013).

The ideal biomarker for acute or chronic kidney disease should show rapid and reliable changes as the disease progresses, be highly sensitive and specific, detect damage to different segments of the nephron, and be rapidly measured.

Biomarkers are classified as prognostic - the likelihood that a patient will develop an endpoint regardless of treatment, or predictive - the likelihood that a patient will respond to a specific treatment. Thus, biomarkers are considered not only as renal biomarkers, but also for oxidative stress, tissue remodeling, metabolism, and cardiac biomarkers (García-Estañ J & Vargas F., 2020).

Serum creatinine remains the most widely used marker of renal function in clinical practice and in clinical trials. Serum creatinine concentration reflects renal filtration, tubular secretion and renal excretion, but also creatinine uptake and metabolism.

Creatinine is a non-enzymatic metabolic product of creatine and phosphocreatine, which under normal conditions is produced by skeletal muscle at a constant rate - about 2% per day of the total creatine reserve. It is a molecule of small molecular mass, is not bound to plasma proteins, is filtered entirely through the glomeruli, is not reabsorbed, but is secreted from the proximal tubules in small amounts that increase with the progression of renal failure.

A disadvantage of creatinine as a biomarker is that it is influenced by factors independent of GFR, such as muscle mass, protein intake, exercise, and drug intake.

In their study, Wołyniec W et al, 2020 refuted that cystatin C is a better indicator of glomerular filtration rate in athletes after exercise than creatinine. Acute damage will not show changes in filtration rate until disease progression leads to its accumulation. In chronic kidney disease, an increase in serum creatinine is a late indicator of a decrease in glomerular filtration rate (Dias C et al., 2022).

EXPOSITION

Conventional biomarkers most often used in practice related to kidney damage in patients at risk can be grouped as - basic analyses, advanced analyses, specialized studies and special low molecular weight proteins.

Basic analyses:

1. Hematological, decreased values of hemoglobin and hematocrit are found due to excretion of erythrocytes in the urine, impaired synthesis of erythropoietin (erythroblastic hematopoiesis). In the differential blood count, increased leukocytes are observed in pyelonephritis - leukocytosis and oiliness, and accelerated ESR (erythrocyte sedimentation rate).

2. Qualitative examination of urine - color, transparency, odor, pH, protein, glucose, sediment, relative weight.

The presence of proteinuria - on account of albuminuria later leads to the omission of proteins of higher molecular mass.

Tubular proteinuria is due to disturbances in the reverse tubular resorption of freely filtered proteins of low molecular mass. It is observed in polycystic kidney disease, infectious diseases - pyelonephritis, renal dysplasia, renal tubular acidosis, acute renal failure, renal infarction. Glomerular proteinuria is due to increased filtration through the capillary wall of the glomerulus and is a marker of glomerular disease (glomerulonephritis, incipient diabetic nephropathy).

The degree of proteinuria does not always correlate with the prognosis of renal disease. Microalbuminuria is a sign of a complication of diabetes - initial diabetic nephropathy. Normally, albumin 30 mg/24h passes through the kidney. Values of 30 to 300 mg/24h. have great diagnostic significance because at this stage the condition is reversible. Hematuria occurs due to damage to the glomerulus, trauma, tumors, stones along the course of the urinary tract, etc. Hematuria can be:
- prerenal (thrombocytopathies, anticoagulant therapy, hemophilia, etc.);
- renal (glomerulonephritis, pyelonephritis, diabetic nephropathy, tumors, diabetic nephropathy, etc.);
- postrenal (stones in the urinary tract, tumors, trauma);
- presence of blood clots /macroscopic/ - excludes glomerular origin;
- small thread-like clots - in case of bleeding from the upper urinary tract /ureter/;
- erythrocyte or hemoglobin cylinders - glomerular origin.

Myoglobinuria - its causes can be: muscle necrosis, surgical interventions, malignant hyperthermia, toxic substances, autoimmune diseases.

Cylinders are a protein cast of the renal tubules. They are always of renal origin, are formed from Tamm Horsfall protein by precipitation and include plasma proteins, lipids, cells, crystals.

Normally no cylinders are found in the urine. The presence of cylinders in the urinary sediment indicates the presence of renal pathology

Advanced analyses:

1. Dilution and concentration - samples are carried out with the tests of relative weight of urine:
- Folhard functional samples;
- Zimnicki assay.

The basic rule is: a kidney that dilutes well - concentrates well!

2. Functional clearances: reflect: the volume of plasma that is completely cleared of a substance per unit time. A decrease in glomerular filtration rate is a major sign of chronic kidney disease.
- Endogenous clearance - with creatinine, urea, electrolytes;
- Exogenous clearance is performed in special clinics, usually the patient must be catheterized.
- GFR (glomerular filtration rate) - glomerular filtration rate represents the best quantitative measure of kidney function, indicates how well the kidneys are filtering blood, allows detection and staging of chronic kidney disease. GFR cannot be measured directly. It is necessary that the measured plasma substance is completely filtered through the glomeruli, not absorbed by the tubules, to be completely emitted by the kidneys. The most suitable for this measurement is creatinine - an excretory product anhydride of creatine phosphate, filtered completely through the glomerulus, not resorbed in the tubule.

3. Quantitative sediment Stansfeld and Webb sediment is carried out when limiting values of form elements are established in the oriented sediment. The form elements are enumerated in a Bürker chamber in a portion of fresh uncentrifuged urine. Haematuria is observed in the presence of more than 8 erythrocytes per 1 μl by the Stansfield-Webb method.

4. Phase-contrast evaluation of erythrocytes:

The presence of 80% dysmorphic erythrocytes - indicates damage to the glomerular membrane. At 20% dysmorphic erythrocytes - directs that the bleeding is from the lower urinary tract.

5. Concentration of urea, creatinine, uric acid in serum.

Urea is filtered in glomeruli, about 40% of it is reabsorbed in tubules therefore not suitable for early diagnosis of kidney disease.

Cretinin values rise from 48-72 hours after the onset of injury. It is a reliable indicator of renal function and glomerular filtration rate due to constant ratio between formation and excretion, excreted entirely by glomerular filtration.

Uric acid - filtered through glomeruli, reabsorbed entirely in proximal tubules, about 2/3 excreted in urine.

6. Selectivity of proteinuria.

- Degree of damage to the glomerular membrane, which leaks proteins of different molecular mass - with the progression of glomerular damage, proteins of different molecular size begin to pass into the urine - non-selective glomerular proteinuria develops.
- Bens Jones protein - over-synthesis of monoclonal immunoglobulin light chains characteristic of multiple myeloma;
- Microalbuminuria - an example of selective glomerular proteinuria, a sign of a complication of diabetes - diabetic nephropathy.

7. Homeostatic function and Acid-base status.

The kidney is a major regulator of sodium homeostasis. Serum sodium concentration is determined by glomerular filtration and tubular resorption. It is regulated by aldosterone and natriuretic hormone. In chronic kidney disease, hyponatremia with hypoosmolality occurs because of restricted water excretion.

In acute kidney injury and chronic renal failure, due to insufficient excretion, there is often hyperkalemia. Hypokalemia is most often observed in theeffect of renal and extrarenal losses.

Serum values of Fe, LSC, and transferrin serve to evaluate anemia of renal origin.

Systemic elevation of CRP (C-reactive protein), an acute phase protein, indicates persistent chronic inflammation at values of 15-30 mg/l.

Specialized research:

- Clearance of exogenous substances - FAH, inulin;
- Determination of renal blood flow;
- Maximum tubular secretion;
- Renin, aldosterone, cortisol, cystatin C;
- Urinary enzymes - lysocin, N-acetyl-β, β-NA G;
- Individual proteins - β2-microglobulin, retinol-binding protein, ά1-microalbumin, erythropoietin, cellular and humoral immunity factors.

Special low molecular weight proteins:

- β2 microglobulin - in serum has a constant level, in urine it is increased in heavy metal poisoning or in drug-induced tubular damage. It is an early indicator of transplant rejection.
- Tamm-Horsfall protein (urinary protein) - up to 25mg/24h, originates from renal interstitial tissue.
- Cystatin C is a protein marker for assessing glomerular filtration rate, rises at 8 hr from onset of injury. Its plasma concentration is unaffected by inflammatory processes, depending only on its synthesis and clearance through the kidney. It is completely filtered through the renal filter and completely resorbed in the proximal tubule.

CONCLUSION

Ideal biomarkers in acute and chronic kidney disease should be highly sensitive, rapid, and specific as the disease progresses. Serum creatinine is a late indicator of decreased glomerular filtration rate and is influenced by a number of external factors, but at this stage there is no more reliable indicator to distinguish between true parenchymal and prerenal azotemia and remains the most widely used marker of renal function in practice. Other laboratory indices such as proteinuria, presence of cylinders in the sediment, and sodium loss have low sensitivity for early detection of acute kidney injury. Complementing basic and advanced analyses with specialized tests and special low molecular weight proteins can aid diagnosis, prognosis and differential diagnosis.

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