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Plasma and Urine Biomarkers in Chronic Kidney Disease

Nabil Ibrahim Khader Samin
University Kirkuk College of Science Department of chemistry

Aseel Abdulazeez Mohammed Ahmed
Anbar University College of Science Chemistry sciences

Saja Ali Muhaibis Faraj
University of Thi Qar College of Science Department of Chemistry

Lubna Hamed Yassin Ismael
University of Diyala College of Science Department of Chemistry

Mustafa Yaseen majeed abd
University Kirkuk College of Science Department of chemistry

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Annotation: General Background: Chronic kidney disease (CKD) is a progressive condition affecting a significant proportion of the global population, characterized by impaired renal function and associated with high morbidity and mortality. Specific Background: The disease often remains undiagnosed in its early stages due to the absence of noticeable symptoms, leading to late-stage diagnosis and limited treatment options. Biomarkers such as urea, creatinine, albumin, total protein, and glucose are commonly used to assess kidney function, yet their diagnostic utility requires further validation. Knowledge Gap: Despite the clinical importance of these biomarkers, there remains insufficient evidence regarding their early diagnostic value and their comparative significance in CKD progression. Aims: This study aims to evaluate the levels of key plasma and urine biomarkers in CKD patients compared to a control group, providing insights into their potential role in early detection. Results: The findings reveal significantly elevated levels of

urea, creatinine, and glucose in CKD patients, while albumin and total protein levels were markedly reduced. Statistical analysis confirmed the significance of these differences, reinforcing their association with CKD pathology. Novelty: This study provides empirical validation of biomarker alterations in CKD, offering a comprehensive comparison of their diagnostic relevance. Implications: The results emphasize the need for improved screening strategies utilizing these biomarkers for earlier detection, facilitating timely intervention and reducing disease progression risks. These insights contribute to refining CKD diagnostic approaches and optimizing patient management strategies.

Keywords: Chronic Kidney Disease, Biomarkers, Urea, Creatinine, Albumin, Glucose, Early Detection.

1-Introduction

1.1- The kidneys

The human body has two kidneys located at the back of the peritoneal cavity, which are vital organs necessary for its proper functioning. The main function of the kidneys is to regulate the balance of salt, water and other ions and trace elements in the human body, such as calcium, phosphorus, magnesium, potassium, chlorine and acids. At the same time, the kidneys secrete hormones. The kidneys are also the site of the action of hormones that are responsible for regulating blood pressure, fluid balance or bone metabolism and vascular calcifications. Finally, the kidneys eliminate all the useless products of metabolism, as well as drugs and other toxins that enter the body [1]. Diabetes and high blood pressure are the two main causes of chronic kidney disease. Diabetes is characterized by high blood sugar levels, causing damage to the kidneys and heart, blood vessels and eyes,and poor control of high blood pressure can be a major cause of heart attack, stroke and chronic kidney disease. Other conditions that affect the kidneys are glomerulonephritis, hereditary diseases, dysplasia, kidney stones, tumours, recurrent urinary tract infections, metabolic diseases, obesity and age [2].

1.2- Chronic kidney disease

The Chronic Kidney Disease (CKD) is a progressive disease with no cure and high morbidity and mortality that occurs commonly in the general adult population, especially in people with diabetes and hypertension [3]. It is a silent disease. Most CKD patients are unaware of their condition during the early stages of the disease which poses a challenge for healthcare professionals to institute treatment or start prevention [4]. CKD involving both non-modifiable (e.g. older age, family history and ethnicity) and modifiable risk factors (e.g. Type two diabetes mellitus(T2DM), hypertension and dyslipidaemia) which are responsible for the initiation of early CKD, CKD progression [5]. In the first three stages, there are no specific symptoms by the virtue of which this disease will be detected easily . But this disease must be detected at the initial or early stages. In the fourth stage of this disease, the functionality of the kidney is very low and the required treatment of this is needed to improve the condition of the kidney. At the

end or fifth stage, the kidney is no longer able to do its tasks properly. It fails to remove the extra water and waste products from the body. This stage is basically known as kidney failure, and there is no cure for this rather than kidney transplant or dialysis. Because chronic kidney disease is asymptomatic, it is difficult to identify until it has progressed, resulting in fewer options for preventing disease [6].The CKD is defined by a low glomerular filtration rate or high albuminuria, and affects 15–20% of adults globally [7], it is decreased kidney function defined by a glomerular filtration rate of less than 60 mL/min/1.73 m2 and/or markers of kidney damage, of at least 3 months duration . Early diagnosis and treatment are two major measures to prevent further deterioration of kidney function and to delay adverse outcomes, However, the paucity of early, predictive and noninvasive biomarkers has undermined our ability to promptly detect . Despite all limitations, kidney function is still measured by serum creatinine, cystatin C, and albuminuria, as well as estimating glomerular filtration rate using different equations [8].

1.3- Biomarkers in Chronic kidney disease

1.3.1- Urea

Urea is a product of protein metabolism that is often used as a proxy for Chronic Kidney Disease CKD severity and dialysis adequacy in clinical settings. Given the dietary origin of a proportion of the urea in the circulation, nutritional therapy could be used to counter an elevation in urea levels [9]. Urea (also known as carbamide), is a volatile organic compound with chemical formula $CO(NH_2)_2$.. Urea serves an important role in the metabolism (and especially catabolism) of nitrogen-containing compounds. Until recently, urea was considered merely as a by-stander compound used to monitor renal function, but not as a toxic agent playing key pathophysiological roles. For the renal community, the uraemic syndrome is considered not to be related to urea alone, but rather to a myriad of other toxins that accumulate in biological fluids as a result of kidney failure. It should be noted that there are several situations, aside from kidney failure, that increase urea levels, including large dietary protein intake, changes in hydration status and intestinal bleeding. Some data suggest that urea is an antioxidant and could protect cells from hypertonic stress [10]. Urea is a facilitating 80–90% of nitrogen elimination from human body. Increased blood urea level indicates impaired renal function, and decreased urea level can be due to poor liver function and protein-energy malnutrition [11].

1.3.2- Creatinine

Creatinine has great limitations when evaluating kidney function in patients with acute pathologies, where its values can change unpredictably and also take time to do so. Another great limitation is its generation because this is a complex process that depends on multiple metabolic steps. During acute kidney injury the increase in serum creatinine is due to a decrease in a glomerular filtration rate and backleak through damaged proximal tubule cells , due to these complex steps, in different clinical scenarios, the increase in serum creatinine does not always represent a true damage to the kidney parenchyma [12]. The creatinineis constantly excreted from the body depending on the mass of protein and muscle metabolism . Kidneys purify blood by filtering its contents and are released into urine. Creatinine is one among the metabolites expelled from the body by the function of kidneys. Its level in body can be checked through blood sample and the high level determines the impairment of kidneys. Protein and muscle mass are also the determining factors of creatinine content in human body; hence men have relatively higher muscle mass and usually contain higher creatinine than woman and children. The creatinine formed in the muscle transported to kidney [13]. Serum creatinine is the anhydride form of creatine and serves a marker of renal function . In clinical studies, elevated serum creatinine levels are generally considered as an adverse events or outcomes, often indicating renal impairment , meanwhile, studies have shown that impaired renal function is often accompanied by increased cardiovascular risk . Serum creatinine levels are strongly associated with longitudinal risk for cardiovascular disease and mortality [14].

1.3.4- Proteins

Serum total protein (TP) occurs as a complex mixture of several proteins including albumin and globulin that are synthesized by the liver and blood cells [15]. Serum albumin has essential antioxidant properties, low albumin to globulin ratio has been associated with vascular adverse events and red blood cell aggregability in both acute and chronic Cardiovascular disease(CVD) , including its risk factors such as old age, diabetes, hypertension, and renal insufficiency [16]. Serum albumin represents approximately half of the total serum protein TSP and is the primary determinant of metabolic homeostasis. Albumin regulates microvascular permeability and plasma oncotic pressure. total serum protein (TSP) is a composite indicator of immunity, nutrition, and metabolic balance by including albumin and globulin [17]. Blood urea nitrogen (BUN) is the main end product of protein metabolism in the human body and is excreted mainly by the kidneys. BUN level will increase when there is excessive protein breakdown or when the glomerular filtration rate decreases. Thus, BUN level can reflect protein catabolism in the human body and is also a marker of renal impairment. The rate of protein catabolism increases significantly in patients with sepsis , and sepsis is often complicated with acute renal injury . These factors can lead to an increase in BUN levels in patients with sepsis. Meanwhile, the BUN test is simple and common in clinical laboratories [18].

1.3.5- Glucose

Glucose is one of the main body fuels and its blood levels are tightly regulated. Plasma glucose values are maintained within a narrow range throughout the day despite wide fluctuations in the delivery and removal of glucose from the circulation in order to fuel the body organs and notably the brain. Gluconeogenesis is the pathway by which glucose is synthesized and is crucial in maintaining normoglycaemia during fasting and stress conditions. After an overnight fast, glucose production relies on endogenous production by both glycogenolysis and gluconeogenesis. Glycogenolysis is the breakdown of glycogen to glucose-6-phosphate and further hydrolysis to glucose. As fasting progresses, glycogen, stored mainly in the liver and the muscles, is depleted. After around 60 h of starvation in humans, gluconeogenesis becomes the only source of glucose production . Gluconeogenesis is classically attributed to the liver. However, in 1937, the ability of the mammalian kidney to produce glucose from non-carbohydrate precursors [19].Fatty Acid Oxidation may be the preferred energy substrate for proximal tubules, but the kidney is an important organ for glucose reabsorption, production, and utilization. Most of the filtered glucose, a total of 180 g per day, is reclaimed by one of two sodium-dependent glucose cotransporters located on the apical surface of the proximal tubule. The kidney and liver are the only two organs capable of releasing glucose into the circulation as other tissues lack glucose 6-phosphatase, required for glucose formation from glucose-6-phosphate. In diabetic patients, there is evidence that gluconeogenesis is further upregulated by both the kidney and the liver . These findings suggest that renal gluconeogenesis may contribute to hyperglycemia in diabetic patients. For diabetic patients with chronic kidney disease, this loss of renal gluconeogenic activity likely contributes to hypoglycemic episodes in addition to reduced insulin clearance that results from impaired kidney function [20].

2- Material & Methods

2.1- The Kits Used

Table (2-1) Ready-made diagnostic kits used

No.	Kits	Company	Country
1	UREA	FUGIFILM	Japan
2	TOTAL PROTEIN	FUGIFILM	Japan
3	CREATININAE	FUGIFILM	Japan
4	ALBUMIN	FUGIFILM	Japan
5	SUGAR	FUGIFILM	Japan

2.2- Instruments Used

Table (2-2) Laboratory tools and equipment used

No.	Devices used	Company	Country
1	Centrifuge	Gallenkamp	England
2	FUJI DRI-CHEM SLIDE	FUJIFILM Europe	Japan

2.3- Samples Collection

Blood samples (30) were collected. The samples included (15 samples from Kidney patients)after they were diagnosed by specialized doctors and (15 samples from the control group) of the female gender only . (5mL) was withdrawn from the vein using sterile medical syringes that are used only once, and Then it was unloaded into clean, sterile plastic gel tubes with a tight cap and free of the anticoagulant EDTA. The blood was left for a quarter of an hour at room temperature, and then the tubes were placed in the centrifuge for a quarter of an hour at a speed of (4000 rpm). After that, then the serum was withdrawn using a fine pipette and placed in a small, sterile plastic tube (Eppendorf Tube) of size (1.5 mL). Then measure the variables.

2.4- Information Questionnaire

.....Pateint name	3	..... Date	2	.....Tube No.	1
..... Height	6	.....Weight	5	.....Chronic diseases	4
..... DM	9	..…phone number	8	..... Occupation	7

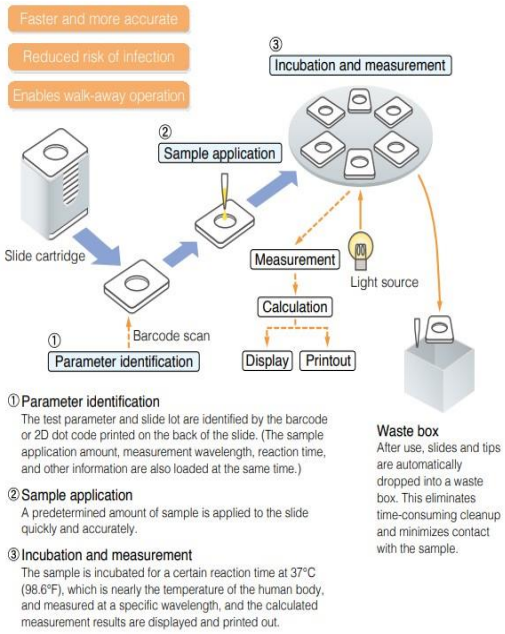
2.5- Principle of the Assay

The working principle of the Japanese chemical analysis device manufactured by FUJI Company, which is considered the latest and most advanced in the field of Dry Chemistry.

1-Colorimetric: Specific to chemical analyses, the slide consists of multiple layers of dried chemical agents (reagents) that will enter into chemical reactions to determine the value of the enzyme or substance to be examined by calculating the value of the change in color occurring in it in a very accurate manner.

2-Potentiometric for electrolytes. Each slide contains ion-selective electrode for each of sodium, potassium, and chlorine. The value of each electrolyte is determined by determining its potential value.

2.6- Procedure



1-We draw blood from people (women, healthy people, and sick people), put it in test tubes to separate the serum, and wait a quarter of an hour for the blood to clump.

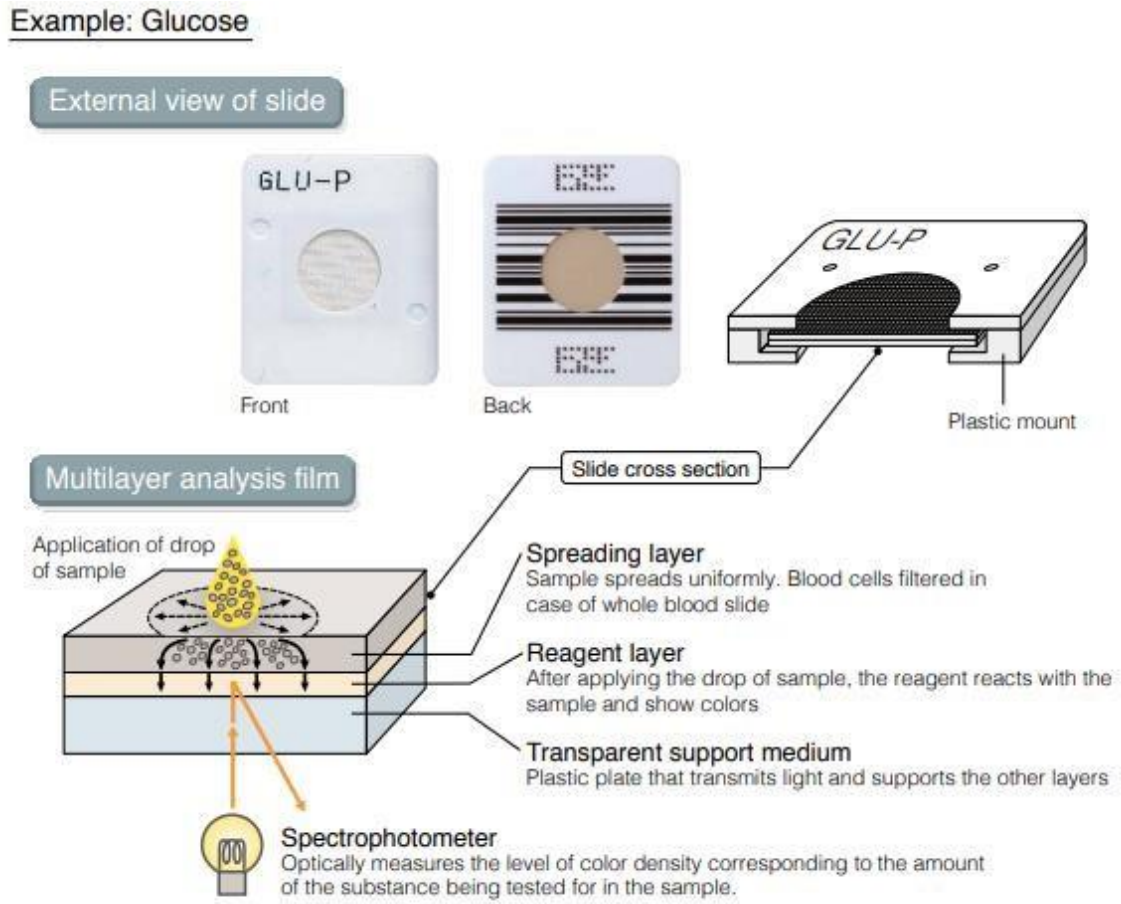
2-We place these samples in the centrifuge device for 5min (4000 rpm), after which we transfer the samples to the Fujifilm device.

3-The Fujifilm device contains a Hitachi cap to place part of the sample in, and it also contains a special cap to transfer the sample to the cassettes. We must also know the device before starting the process on the barcot ketate that we need, which is urea. Sugar . Creatinine. Albumin. Total protein. Then we enter sample information such as the sample number. The type of analysis and the gender of the sample. The samples were women

4-We withdraw part of the blood serum sample using a tube, approximately 300 microliters, and place it inside the Hitachi cap.

5-The device withdraws the special cloth placed in the designated place, withdraws part of the sample, and then places it on the trays

6-Then we get readings from the device



2.7- Reference Values

a- Suger (90-130)mg/dL b- Urea

(16.6-48.5) mg/dL c- Creatinine (0.4-1.4) mg/dL d- Total Protein (6.0-7.8) g/dL e- Albumin (3.4-4.8) g/dL f- Globulin

The concentration of globulin was estimated mathematically in units of (g/dL) using the equation Glo.=TP-Alb. [21]

(2-3.5)g/dL [22]

2.8- Statistical Analysis

The statistical analysis program known as the Statistical Package for the Social Sciences (SPSS) (Tow-Sample T-test or independent samples T-test) was used by comparing the group of patients with Chronic kidney disease with the control group to find out (Std. Error of Mean) and (Mean) and probability level (P-value). The value P≤ 0.05 was taken as a normal statistical value, and the value P≤ 0.01 was taken as a high statistical value.

3-Results & Discussion

3.1- Results

Table (3-1) Level of vital indicators in the blood serum of the groups under study

Parameters	Healthy	Patient	P -value
Urea	31.09 ± 1.725	(142.1± 11.69)**	< 0.0001
Parameters	Healthy	Patient	P -value
Creatin	0.5953± 0.027	(7.4± 0.515)**	< 0.0001
Parameters	Healthy	Patient	P -value
TP	7.5± 0.087	(6.3± 0.192)**	< 0.0001
Parameters	Healthy	Patient	P- value
Alb	4.887± 0.08	(3.6± 0.12)**	< 0.0001
Parameters	Healthy	Patient	P -value
Glo	2.63± 0.08	)2.66± 0.17)ns	0.876
Parameters	Healthy	Patient	P- value
BUN	14.16± 0.83	(62.7± 6.233)**	< 0.0001
Parameters	Healthy	Patient	P -value
Sugar	101.0 ± 4.285	214.1± 19.02	< 0.0001

**High statistical differences (P≤0.01) // *Normal statistical differences (P≤0.05(nsThere are no significant differences (P>0.05)

3.2- Discussion

- The results showed, as shown in Table (3-1), that the Suger concentration level is in (mg/dL) using)Std. Error of Mean(increases in CKD patients with a highly significant increase at the probability level (P=0.0001) when compared to the control group. The monitoring of glycemic status in patients with diabetes and CKD including is challenging. HbA1c, the gold standard as a laboratory glycemic marker, can be influenced by multiple factors in CKD. The formation of hemoglobin A1c (HbA1c) is dependent on the intensity and duration of non-enzymatic interaction between blood glucose and hemoglobin. At any one time, patients may have a mixture of erythrocytes with different ages and varying degrees of exposure to glucose. Therefore, agents that alter erythropoiesis and lifespan of red blood cells will affect HbA1c. For example, HbA1c can be biased towards high values by iron or vitamin B12 deficiency due to reduced synthesis of red blood cells with increased relative amount of HbA1c. On the other hand, HbA1c can be biased towards low values by iron therapy and use of erythropoietin stimulating agents with increased turnover of red blood cells [23].
- The results, as shown in the table above, showed that the urea concentration level was (mg/dL) using)Std. Error of Mean(is increased in CKD patients with a highly significant increase at the probability level (P = 0.0001) compared to the control group. Our findings are in line with the current body of epidemiological evidence on kidney function biomarkers and the risk of CVD, and suggest that urea should be taken into account when seeking to predict and prevent cardiovascular (CV) disease in patients with CKD.The BUN, which reflects only the nitrogen content of urea, are routinely used in clinical settings to evaluate kidney function. Urea is the main metabolite derived from dietary proteins and tissue protein

turnover. The compound is almost exclusively excreted by the kidneys in the urine, after filtration in the glomerulus and a certain degree of reabsorption from the filtrate. Although several nonrenal factors affect the serum urea concentration , reduced urinary elimination of urea (due to CKD) is the main factor that increases serum urea levels. Volume depletion by diuretics or a decrease in the effective circulating volume induced by heart failure might contribute to the elevation of urea levels in our CKD patients [24]. The urea levels found in the serum of CKD patients directly increase levels of reactive oxygen species and oxidative stress in several types of cells [25]. Interestingly, endothelial progenitor cell number and function decrease with advancing CKD [26] , which might be due to the acceleration of senescence in endothelial progenitor cells by ureainduced reactive oxygen species [27].

- The results, as shown in the table above, showed that the level of creatinine concentration (mg/dL) using (Std. Error of Mean) was increased in patients with chronic kidney disease with a highly significant increase at the probability level (P = 0.0001) compared to the control group. serum/plasma creatinine is one of the most common laboratory analyses performed in routine clinical practice in CKD. In patients with renal failure, depending on the stages of failure, the waste products (creatinine and urea) can accumulate in the body. Creatinine (2-amino-1-methyl-2-imidazoline-4-one) is the final metabolic product of creatine in muscle,which is converted to creatinine approximately 2% daily at a constant rate. The conversion is spontaneous and irreversible, which finally is excreted through the urine flow. Creatinine is a nontoxic substance with no significant role in biometabolism with controlled concentration by renal excretion. The amount of creatinine in the serum and urine is related to muscle mass and renal elimination, which is relatively stable in serum.Creatinine filtration is performed in the kidney without reabsorption. Therefore, all of the creatinine produced by the contraction of the muscles is extruded from the body through the urinary tract. The serum concentration of creatinine is an important biomarker for kidney failure detection, glomerular filtration rate, and muscular dystrophy [28]. Significant increases in the concentration of serum-derived urea and creatinine (urea: as a reference for low-molecular mass toxic solutes; creatinine: as a reference for toxic molecules of intermediate size), which are metabolic waste products of protein metabolism, are important markers for kidney dysfunction [29]. measuring the creatinine and urea concentration with a faster, more accessible, cost-benefit, and accurate method results in earlier diagnosis approaches and optimum management of patients with kidney disease [30].
- The results, as shown in the table above, showed that the concentration level of total protein and albumin (g/dL) using (Std. Error of Mean) decreased in patients suffering from chronic kidney disease and in a very significant way in the probability level (P = 0.0001) compared to the control group,and no change in globulin level. Serum albumin is the main protein in plasma with a high solubility. It regulates the vascular osmotic pressure, helps transport a variety of endogenous and exogenous substances, and affects the pharmacokinetics of several drugs. Moreover, serum albumin is a vital extracellular antioxidant [31]. Previous researchers have found that decreased serum albumin is an important risk factor for a series of diseases. Quite a few studies have so far proved that lowered serum albumin is a risk factor for patients with CKD [32].

Conclusion

The findings of this study highlight significant biochemical alterations in chronic kidney disease (CKD) patients, notably elevated levels of sugar, urea, creatinine, and blood urea nitrogen, alongside reduced concentrations of albumin and total protein. These results emphasize the critical role of metabolic dysfunction in CKD progression and its association with comorbidities such as diabetes and hypertension. The study underscores the necessity of early biomarker detection for improved disease management and intervention strategies. The implications of these findings suggest a need for comprehensive metabolic monitoring in CKD patients to mitigate complications and enhance treatment outcomes. Future research should focus on the

development of more sensitive and non-invasive biomarkers for early CKD detection and explore targeted therapeutic strategies to address the metabolic imbalances identified in this study.

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