REVIEW ARTICLE

Diagnostic Advancement Versus Traditional diagnosis of Kidney Diseases in Unani Medicine: Novel Biomarkers and Future Prospects

Tayyaba Khatoon[1], Ataullah Fahad[1], Naved Ahmad[2], Veena Gupta[2]

ABSTRACT

Kidney health is critical for waste excretion, acid-base regulation, and hormone production. Lifestyle changes, including poor diet and inactivity, have increased risks kidney diseases. The study on Global Burden of Disease highlights the significant rise in death due to kidney failure, with approximately 1.2 million annual fatalities and millions more are suffering from kidney disease (KD) or acute kidney injury. KD is now a leading cause of death worldwide, particularly in India. The 2024 World Kidney Day emphasizes equitable access to kidney care. In Unani medicine, kidney diseases have long been recognized, with detailed descriptions of their functions and pathophysiology. Assessment methods for kidney function include glomerular filtration rate (GFR) estimation and proteinuria detection. Novel biomarkers such as cystatin-C, NGAL, KIM-1, and SDMA offer enhanced early detection and monitoring of kidney disease. Despite advancements, challenges in early diagnosis remain. Integrating these biomarkers into clinical practice holds the promise of better patient outcomes by enhancing diagnosis and enabling precision medicine. Continued research and standardized protocols are essential for maximizing their diagnostic potential.

Keywords: Kidney diseases, biomarkers, glomerular filtration rate, unani medicine

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INTRODUCTION

Kidney is one of the vital organs responsible for several important functions, such as excreting waste products, regulating acid-base balance, maintaining salt-water balance and producing renin, erythropoietin. With changes in lifestyle patterns, such as unhealthy diets and physical inactivity, many lifestyle-related diseases have emerged, including diabetes and hypertension, which can lead to kidney failure[1].

Additionally, many antibiotics, anticancer drugs, and other synthetic molecules used to treat various ailments in the modern era have inherent adverse effects on the kidneys. A number of therapeutic agents can negatively impact kidney function, leading to conditions such as acute renal failure, chronic interstitial nephritis and nephrotic syndrome[2].

EPIDEMIOLOGY

Based on the Global Burden of Disease (GBD) study conducted in 2015, an approximate of person dying from kidney failure is around 1.2 million, reflecting a 32% increase since 2005. In 2010, it was estimated that between 2.3 and 7.1 million people with end-stage renal disease (ESRD) died due to limited access to chronic dialysis. Furthermore, people around 1.7 million are believed to die each year from acute kidney injury. Overall, it is estimated that 5 to 10 million patients die annually from kidney disease[3]. The incidence of Chronic Kidney Disease (CKD) or kidney failure has doubled in the last 15 years.

1. Department of Ilmul Amraz, Faculty of Unani Medicine, AMU, Aligarh, 202002, UP, India.
2. Department of Biochemistry, F. H. Medical College, Etmadpur, Agra, 283204, UP, India.

Correspondence to: Naved Ahmad, Department of Biochemistry, F.H Medical College, Etmadpur, Agra, 283204, UP, India. Email: drnavedahmad@gmail.com

In India, approximately 7.85 million people are suffering from kidney diseases. Globally, an estimated 850 million people have kidney diseases from various causes, with chronic kidney disease causing at least 2.4 million deaths annually. CKD is now the 6th fastest growing cause of death worldwide. These figures are particularly concerning as many cases in India, which is home to 17.76 % population of the world, remain largely undocumented and unregistered[4].

The theme for World Kidney Day 2024 is "Kidney Health for All – Advancing Equitable Access to Care and Optimal Medication Practice." This campaign aims to raise awareness about the critical need for equitable access to appropriate treatment and care for individuals with kidney disease. The goal is to enhance their quality of life and slow the progression of the disease by addressing disparities in access to medical advancements. In the year 2006 first time the World Kidney Day was observed, with approximately 66 countries participating in various awareness programs. Within two years, this number grew to 88 countries, reflecting the increasing global recognition of the kidney health importance.

UNANI CONCEPT OF RENAL FUNCTION

Unani physician Hippocrates (460-375 BC) was skilled in diagnosing diseases through detailed urine analysis. Artaeus of Cappadocia (30-90 AD) and Galen also recognized the kidney as one of the vital organ responsible for the formation of urine[5].

In the Unani system, each organ possesses four essential faculties: Quwwat-e-Hazimah (digestive power), Quwwat-e-Jazibah (absorptive power), Quwwat-e-Masikah (retentive power), and Quwwat-e-Dafeah (eliminative power). These faculties collaborate harmoniously to uphold the normal function and integrity of the organs. Moreover, the kidney boasts a distinctive faculty termed Quwwat-e-Mumayyizah (separating and distinguishing power). This unique capability enables the kidney to segregate blood from impurities and waste materials, which arise from the body's metabolic processes, intentional administration of therapeutic substances, or inadvertent exposure to environmental toxins. Once this segregation process concludes, Quwwat-e-Dafeah aids in promptly expelling the wastes[6,7].

This intricate mechanism underscores the concerted efforts and synchronization of multiple forces to sustain kidney function and shield it from the constant barrage of waste and toxins. These efforts ensure that harmful substances are swiftly removed, preventing prolonged contact that could lead to kidney damage[8].

When QuwwateMasikah (the body's retaining power) becomes weak or altered, blood and fluids pass through the body without being properly metabolized because they were not given sufficient time to undergo Istahalah (metabolism). Consequently, the action of QuwwateHazimah (the digestive power) is bypassed. When QuwwateHazimah is weakened or altered, the kidneys cannot extract nutrients from the blood, which also carries water and waste matter. If the QuwwateMumaiyyazah (the discerning power) of the kidneys becomes impaired, the kidneys lose their ability to distinguish between essential and toxic substances of metabolism. This results in the excretion of valuable nutrients through urine, while toxic substances remain in the body[9].

CLASSIFICATION OF KIDNEY DISEASE

Ancient unaniphysicians classified kidney diseases into four types of major categories i.e. Amraz-e-Sue Mizaj, Amraz-e-Sue Tarkeeb, ,Amraz-e-Tafarruq-e-Ittesal, Amraz-e-Sudda

1) **Amraz-e-Sue Mizaj:** Normal *mizaj*(temperament) is *harratab*(hot and moist) of kidney.Any deviation from the normal physiological temperament of the kidneys can produce various pathological conditions, depending on the extent and type of deviation. These conditions are as follows:: (i) *Sue mizajhar*(abnormal hot temperament), implies when temperament of the kidney surpass its normal hot temperament. (ii) *Sue mizajbarid*(abnormal cold temperament), normally, the kidneys do not have a cold temperament. However, in certain diseased conditions, a relatively lower degree of heat than the normal physiological temperament is considered cold. (iii) *Sue mizajratab*(abnormal moist temperament), The normal temperament of the kidneys is also moist, and any excess in this moisture can lead to disease.. (iv) S*uemizajyabis*(abnormal dry temperament), This implies that when the kidneys acquire dryness, deviating from

their normal moist temperament, it results in a pathological state.[10,11].(IbnSina, 2007, IbnZuhar 1986).

2) **Amraze Sue Tarkeeb:** In this state there is malformation of the kidneys, occurs due to three abnormalities: amraz-e-khalqat (structural abnormalities), amraz-e-miqdarwaadad (malformation in number and size) and amraz-e-waza (deformity in the kidney arrangement)[10].

3) **AmrazeTafarruqueIttesal:** This is a acquired pathological affliction of the kidney which essentially arises from tissue injury due to trauma, wounds, or rupture of the blood vessels, leading to a loss of the organ continuity. The deformities can occur in the kidney or in its tubules[10].

4) **AmrazeSudda:** Sudda refers to an obstruction affecting any part of the kidney, most commonly the ducts, tubules and vessels. This narrowing can be caused by a stone, blood clot, abnormal growth, or tumor, leading to disease in the kidney[10].

Zauf-e-kuliya: When the kidney's absorption capacity diminishes, it can lead to symptoms such as frank haematuria (blood in the urine) and ascites. Occasionally, this weakening of the absorptive function occurs due to an accumulation of excessive waste products[12].

Azam Khan describes Zauf-e-Kulliya as a condition where the kidneys are either completely or partially unable to fulfill their functions. According to other Unani physicians, inability of kidney to execute normal filtration process may arise from Quwwat-e-Masika (Retentive faculty) or Quwwat-e-Hazima (Digestive faculty) weakness, leading to the emergence of Ghussali (blood-stained) urine[13].

Zauf-e-kuliya is an important disease of kidney mentioned in Unani literature, Unani physicians have characterized Zauf-e-Kulliya as a condition wherein the kidneys lose their ability to effectively filter water and other substances from the blood, resulting in their passage, unaltered, into the urinary bladder. This blood, originating from the liver, enters the kidney and contributes to the diluted urine, which may contain proteins[14,15].

Qarshi: Qarshi also described a condition Sammiyat-e-Baul (toxic urine) characterized by the accumulation of urinary toxic substances in the bloodstream, affecting the nervous system and potentially leading to symptoms such as coma and delirium[14].

The above statements clearly indicate that ancient Unani scholars had an understanding of kidney disease since antiquity. They were not only able to diagnose these conditions but also treated them successfully.

Pathophysiology: While discussing the pathophysiology of Kidney Disease (KD), it's essential to consider its physiological characteristics, structure as well as the principles of its tissue injury and repair. Firstly, the renal blood flow rate of 400 ml/100g of tissue/ minapproximately surpasses that was also observed in other well-perfused vascular beds such as the liver, heart and brain. This high flow rate exposes renal tissue to significant quantities of potentially toxic substances. Secondly, glomerular filtration depends on relatively high trans and intraglomerular pressure, making glomerular capillaries susceptible to hemodynamic injury compared to other capillary beds. Glomerular hyperfiltration and hypertension have been recognized as significant contributing factors to the advancement of KD. Thirdly, the glomerular filtration membrane contains negatively charged molecules that serve as a barrier against anionic macromolecules. Disruption of this electrostatic barrier, seen in various forms of glomerular injury, allows plasma proteins to access the glomerular filtrate. Fourthly, the sequential organization of the nephron's microvasculature and the downstream position of the tubules with respect to glomeruli maintain glomerulo-tubular balance and facilitate the spread of glomerular injury to the tubulointerstitial compartment, exposing tubular epithelial cells to abnormal ultrafiltrate. Mediators of glomerular inflammatory reactions may overflow into the peritubular circulation, which contributes to the interstitial inflammatory reaction common in glomerular disease. Moreover, any reduction in preglomerular or glomerular perfusion results in diminished peritubular blood flow, potentially inducing tissue remodeling and consequentlytubulointerstitial injury. The glomerulus should also be viewed as a functional entity, where each of its components contributes significantly to normal function. Injury to one component can impact others through various mechanisms, including direct cell-cell connections and soluble mediators.

The primary factors contributing to renal injury encompass immunologic reactions (stimulated by immune cells or immune complexes), tissue hypoxia and ischemia, exogenous agents such as drugs, endogenous substances like paraproteins or glucose, and genetic defects. Tubulointerstitialfibrosis andGlomerulosclerosis are prevalent characteristics of KD, irrespective of its root cause.

Unani pathophysiology: Unani scholars attributed following pathological changes inzauf-e-kuliya for the deterioration of renal functions

- Sue mizajharmustehkam (Stable & hot disorder in the temperament) of kidney
- Amraz-e-sue tarkeeb (Deformity in shape and size) ofkidney making it soft or loose in consistency and enlargedin size
- Amraz-e-suddahwamujari (Urinary tract deformity orobstruction) causing dilatation and hypertrophy of renaltubules, vessels and capillaries
- Weakness either in any of the one (Quwwat-e-jazibah, quwwat-emasikah, quwwat-e-hazimahquwwat-e-mumayyizah)of kidney

Ijtima-e-qiwaam-e-gurda (Deposition in renal matrix)It is noticeable that majority of Unani scholars considereddilatation and hypertrophy of renal tubules and capillaries,deposition in renal matrix, excessive quantity of fluid enteringkidney, soft and enlarged kidney mass as principlepathological changes in zauf-e-kuliya. Clearly, these changesare found in accordance with modern pathology viz.glomerular hypertrophy, hyperfiltration and increase ofmesangial matrix involved in nephropathy[9-11,17-,23].

SPECIMEN COLLECTION

The requirements for specimen collection depend on the specific procedure or test which is requested. Typically, for measuring serum levels of creatinine and blood urea nitrogen (BUN), no specific patient preparation is necessary, and a random sample of blood is adequate. However, recent high protein intake can significantly elevate serum levels of creatinine and urea. Additionally, hydration status can greatly influence BUN measurement. In timed urine collections cases, such as the 24-hour urine creatinine clearance test, it is crucial to accurately collect urine over the specified period. Inaccurate collection, either too little or too much, can affect the final results. Therefore, a timed collection span of 5 to 8 hours is preferable over a 24-hour collection period.[24,25,26] The collection of midstream urine is important for urine analysis as this sample is likely to be less contaminated by cells such as epithelial cells and commensal bacteria.

PROCEDURE

Assessment of Renal Function: There are various clinical laboratory tests available for evaluating and investigating kidney function. Clinically, the most practical tests to assess renal function include estimating the glomerular filtration rate (GFR) and detecting for proteinuria (albuminuria).

Glomerular Filtration Rate: The glomerular filtration rate (GFR) is one of the best overall indicator of glomerular function. It measures the rate, in ml/ minute, at which any substances present in plasma are filtered through the glomerulus. For an adult male, the normal GFR ranges from 90 to 120 ml/min. An ideal marker for GFR should:

- Appear in the plasma at a constant rate
- Freely filtered at the glomerulus
- Neither secreted nor reabsorbed by the renal tubule
- Also, neitherundergoextrarenal elimination.

Since such marker which is endogenous does not exists, exogenous markers of GFR are used. The reference method for estimating GFR involves inulin infusion and measurement of levels in blood after specific period to determine its clearance rate. Other exogenous markers include radioisotopes like chromium-51 ethylene-diamine-tetra-acetic acid (51Cr-EDTA) and technetium-99-labeled diethylene-triamine-pentaacetate (99Tc-DTPA). The contrast agenti.e non-radioactive, iohexol is especially promising, particularly for use in children.

Endogenous Markers: Due to the inconvenience and complexity of using exogenous markers, endogenous markers such as creatinine are more commonly used.

Creatinine: Creatinine is the most commonly utilized endogenous marker for evaluating glomerular function. The creatinine clearance test, which involves collecting urine over a defined period and calculating clearance based on urinary and plasma concentrations, serves as an indicator of GFR. However, this method can overestimate

GFR by 10% to 20% due to tubular secretion of creatinine. Additionally, factors such as muscle mass, dietary intake, and pregnancy can influence creatinine levels, making serum creatinine a late marker of renal dysfunction.

Estimating Equations: Serum creatinine is used in GFR estimating equations such as the Modified Diet in Renal Disease (MDRD) and the CKD-EPI equations, which adjust for race, age, and gender. These equations classify GFR into the following stages based on kidney disease:

- **Stage 1:** GFR > 90 ml/min/1.73 m²
- **Stage 2:** GFR 60-89 ml/min/1.73 m²
- **Stage 3a:** GFR 45-59 ml/min/1.73 m²
- **Stage 3b:** GFR 30-44 ml/min/1.73 m²
- **Stage 4:** GFR 15-29 ml/min/1.73 m²
- **Stage 5:** GFR < 15 ml/min/1.73 m² (ESRD)

Blood Urea Nitrogen (BUN): BUN is a nitrogen-containing compound formed in the liver, and about 85% of it is eliminated via kidneys. Serum urea levels increase with decreased renal clearance and can also be influenced by non-renal factors. The BUN: creatinine ratio helps differentiate between pre-renal and renal causes when BUN is elevated.

Cystatin C: Cystatin C is a low-molecular-weight protein produced at a constant rate by all nucleated cells. Its serum levels are inversely correlated with GFR and are not affected by age, muscle bulk, or diet. Cystatin C can be more reliable than creatinine in early renal impairment and is incorporated into the combined creatinine-cystatin KDIGO CKD-EPI equation. However, cystatin C levels can be influenced by cancer, thyroid disorders and smoking.

Albuminuria and Proteinuria: Albuminuria term indicates the presence of plasma protein albumin in the urine and is a marker for detecting incipient nephropathy in diabetics and chronic renal impairment. Persistent albuminuria for three months or more indicates chronic kidney disease. The KDIGO classification defines three stages of albuminuria:

- **A1:**< 30 mg/g creatinine
- **A2:** 30-300 mg/g creatinine
- **A3:**> 300 mg/g creatinine

Urinary Analysis: Urine analysis involves assessing physical, chemical, and microscopic characteristics. The physical inspection includes evaluating color and clarity. Specific gravity, measured using refractometry or dipstick, indicates renal concentrating ability. Dipstick tests provide qualitative analysis of various analytes and microscopic analysis assesses cells, casts and crystals in the urine[27].

NOVEL BIOMARKERS

Recent advancements have introduced a variety of novel biomarkers that enhance the precision and sensitivity of diagnosing CKD. These new markers provide insights that go beyond, and for early detection than traditional measurements, greatly improving the accuracy and effectiveness of risk stratification. One such marker, the urinary albumin-to-creatinine ratio (UACR), has proven to be particularly predictive of kidney damage. Its ability to detect even small percentage increases in albuminuria makes it an effective for early identification of kidney impairment and for monitoring disease progression. Although albuminuria is critical for assessing disease progression, it is less frequently evaluated in clinical settings compared to the estimated glomerular filtration rate (eGFR)[28]. Early stages of kidney disease often present with minimal symptoms and are typically associated with a normal or elevated eGFR,necessitating laboratory testing for accurate detection. Proper diagnosis of CKD using UACR is crucial, especially in the early stages of the disease[29].

Numerous studies have highlighted neutrophil gelatinase-associated lipocalin (NGAL) as a significant marker for detecting chronic and systemic kidney disorders, renal tubular damage, non-communicable systemic inflammatory response syndrome, and bacterial infections [30]. The primary sources of NGAL in the body include the collecting ducts, the loop of Henle, and leukocytes[31]. Urinary NGAL has been shown to be a reliable indicator of renal injury, often before any noticeable changes in eGFR are evident[32].

Kidney injury molecule-1 (KIM-1) is another important biomarker for detecting subtle cellular damage in the kidney. It is upregulated in the proximal tubules following ischemia or toxic injury[33,34]. Urinary KIM-1 is considered a precise

indicator of kidney damage, often detectable before any significant alterations in eGFR occur[35]. It has been suggested as a potential biomarker for chronic renal disease resulting from kidney damage.

Symmetric dimethylarginine (SDMA), a stable byproduct of protein metabolism involving arginine, plays a crucial role in basic cellular metabolic functions. The kidneys primarily eliminate SDMA from the body[36]. Factors such as muscle mass, diet, inflammation, blood glucose levels, and estrogen medications do not significantly affect SDMA levels [37]. Additionally, variables like obesity, age, gender, and polycystic ovarian syndrome (PCOS) have only a minor impact on SDMA concentrations[37]. One of theadvantage of using SDMA as a diagnostic marker is that it has low biological variability (5.8%) making it more consistent than other markers[38].

Proteomic markers have the potential to facilitate a more precise and earlier diagnosis of renal disease compared to traditional indicators such as creatinine and urine albumin[39]. Many of the indicator peptides in urine are the result of proteolytic activity, making it possible to detect disease-induced changes by analyzing these proteolytic fragments [40].

CHALLENGES AND FUTURE PROSPECTS

Despite advancements in diagnostic methods, several challenges remain. In resource-limited settings, the lack of access to advanced imaging and biomarker assessments hampers early detection of kidney disease. Additionally, integrating new biomarkers and imaging techniques into routine clinical practice requires the development of standardized protocols and guidelines to ensure reliable and accurate interpretation. The growing field of precision medicine presents promising opportunities for improving kidney disease diagnosis.

CONCLUSION

To conclude, the combination of novel biomarkers with traditional indicators allows for a more comprehensive assessment of kidney disease status. These biomarkers enhance diagnostic capabilities and play a crucial role in risk prediction and monitoring disease progression. While the potential of these biomarkers is clear, it is essential to evaluate their sensitivity, specificity and applicability across different patient populations. Continued research and validation are needed to fully harness their diagnostic potential. Overall, the introduction of novel biomarkers marks a significant advancement in the precision and early detection of kidney disease, equipping physicians with better tools for proactive treatment and improved patient outcomes.

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REFERENCES

1. Javaid R, Javed G, Javaid R, Anju, Asim Ali Khan AA. Concept of kidney disorders & its treatment in unani system of medicine. Int J Health Sci Res. 2020;10(9):290-5.
2. Rana MA, Nasiruddin M, Khan RA, Khan AA. Evaluation of nephroprotective activity of ethanolic extract of Bauhinia purpureain gentamicin induced nephrotoxicity in rats. Int J Pharm Sci Res. 2014;5(9):3891-96.
3. Luyckx VA, Tonelli M, Stanifer JW. The global burden of kidney disease and the sustainable development goals. Bull World Health Organ. 2018;96(6):414-22.
4. Quddusi N, Bilal Ahmad, UsamaAkram, Mohammad Fazil, AA Khan. "Concept and Management of Nephritis (Waram- i Kuliya) in Unani Medicine". Acta Scientific Medical Sciences.2020;4(9):129-32.
5. Brenner BM. The Kidney. 6th ed. New York: WB Saunders; 2000. p.1563-4.
6. Khan MA. Ikseer-e Azam. 2nd ed. New Delhi: Aejaz Publishing House; 2003. p.1161.
7. Tabari R. Firdousul Hikmat. New Delhi: Faisal Brothers; 2006. p.240-244.
8. Ibne Rushd. Kitab-ul-Kulliyat. 2nd ed. New Delhi:

CCRUM; 1987. p.226, 302, 111, 112,133

9. Ibn Rushd. Kitab-ul-Kulliyat, 1st ed. New Delhi: CCRUM; 1982. p.27, 87, 112.
10. Ibn Sina. Al Qanoon Fit-Tibb, (Urdu trans Kantoori GH), 1st ed. part-I, Vol. 2, New Delhi: Idara Kitabush Shifa; 2007. p.105.
11. IbnZuhr A.M. Kitab al-Taisir fi al-Mudawatwa al-Tadbir, New Delhi: CCRUM; 1986. p.159.
12. Ibn Zuhr AM. Kitab al-Taisir fi al-Mudawatwa al-Tadbir. New Delhi: CCRUM; 1986. p.158-63.
13. Khan MA. Ikseer-e Azam. (Urdu translation by Kabiruddin), Rawalpindi: Tibbi Co; 1940. p.1189-1226.
14. Qarshi MH. Jamiul Hikmat. V-III. Lahore: Sheikh Mohd Bashir & Sons; 1929. p.750-70.
15. Ibn-e-Sina.AlQanoon Fit Tibb. (urdu translation by GhulamHasnainKantoori) Vol.II . Lahore, Pakistan. Sheikh Mohammad Bashiir & Sons; 1927. p.102-3,159-63.
16. Matovinović MS. Pathophysiology and classification of kidney diseases. EJIFCC. 2009;20(1):2-11.
17. Khan GJ. Makhzan-e-Hikmat, Vol. II. New Delhi: Aijaz Publishing House; 1996. p.650-57.
18. Jurjani AH. ZakheeraKhwarzamShahi,(Urdu trans by Haadi HK), 1st ed, New Delhi: Idara Kitabus Shifa: 2010. p.107,226.
19. Khan MA. Ikseer-e-Azam (Urdu trans. Hkm Kabeeruddin). New Delhi: Aijaz Publishing House; 2010. p.685-91,705-9.
20. Majoosi Ali Ibn Abbas. Kamil us Sana'ah,(Urdu translation by Kantoori GH), 1st ed. New Delhi: Idara Kitabush Shifa; 2010. p.154 ,467,472.
21. Masihi, A.A.F.I.Q (YNA). Kitabul Umdah Fil Jarahat (Urdu translation), 1st Ed. vol-1st, New Delhi: CCRUM; p.130.
22. Rhazi Z. Kitabul Mansoori, 1st ed. (Urdu translation), New Delhi: CCRUM; 1991. p.375,380.
23. Samarqandi N. Sharah Asbab (Urdu trans. Hkm. Kabiruddin), Vol. III, New Delhi: Aijaz Pulishing House; 2007.p. 17-20, 29-36.
24. Gai Z, Wang T, Visentin M, Kullak-Ublick GA, Fu X, Wang Z. Lipid Accumulation and Chronic Kidney Disease. Nutrients. 2019;11(4):722.
25. Kamianowska M, Szczepański M, Wasilewska A. Tubular and Glomerular Biomarkers of Acute Kidney Injury in Newborns. Curr Drug Metab. 2019;20(5):332-49.
26. Wiles K, Bramham K, Seed PT, Nelson-Piercy C, Lightstone L, Chappell LC. Serum Creatinine in Pregnancy: A Systematic Review. Kidney Int Rep. 2019;4(3):408-19.
27. Gounden V, Bhatt H, Jialal I. Renal Function Tests. 2023 Jul 17. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.
28. Collins AJ, Foley RN, Chavers B, Gilbertson D, Herzog C, Johansen K et.al, United States Renal Data System 2011 Annual Data Report: Atlas of chronic kidney disease & end-stage renal disease in the United States. Am J Kidney Dis. 2012;59(1 Suppl 1):A7, e1-420.
29. Levey AS, Becker C, Inker LA: Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: A systematic review. JAMA. 2015;313(8):837-46.
30. Schmidt-Ott KM, Mori K, Li JY, Kalandadze A, Cohen DJ, Devarajan P, et al. Dual action of neutrophil gelatinase-associated lipocalin. J Am SocNephrol. 2007;18(2):407-13.
31. Jayasinghe SS, Jayasumana C, Asanthi HB, Perera HS, Chaminda GG, Chandana EP, et al. Urinary Biomarkers KIM-1 and NGAL for Detection of Chronic Kidney Disease of Uncertain Etiology (CKDu) among Agricultural Communities in Sri Lanka. PLoS Negl Trop Dis. 2016;10(9):e0004979.
32. Zeisberg M, Neilson EG. Mechanisms of tubulointerstitial fibrosis. J Am SocNephrol. 2010;21(11):1819-34.
33. Humphreys BD, Xu F, Sabbisetti V, Grgic I, MovahediNaini S, Wang N, et al. Chronic epithelial kidney injury molecule-1 expression causes murine kidney fibrosis. J Clin Invest. 2013;123(9):4023-35.
34. Sayanthooran S, Magana-Arachchi DN, Gunerathne L, Abeysekera T: Potential diagnostic biomarkers for chronic kidney disease of unknown etiology (CKDu) in Sri Lanka: A pilot study. BMC Nephrol. 2017;18:31.
35. Han WK, Bailly V, Abichandani R, Thadhani R, Bonventre JV: Kidney injury molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney Int. 2002;62(1):237-44.
36. Martens-Lobenhoffer J, Bode-Böger SM. Amino acid N-acetylation: metabolic elimination of symmetric dimethylarginine as symmetric N(α)-acetyldimethylarginine, determined in human plasma and urine by LC-MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci. 2015;975:59-64.
37. Hokamp JA, Nabity MB: Renal biomarkers in domestic species. Vet Clin Pathol. 2016;45(1):28-56.
38. Reinhard M, Erlandsen EJ, Randers E: Biological variation of cystatin C and creatinine. Scand J Clin Lab Invest. 2009;69(8):831-6.
39. Guay C, Regazzi R. Circulating microRNAs as novel biomarkers for diabetes mellitus. Nat Rev Endocrinol. 2013;9(9):513-21.
40. Candiano G, Musante L, Bruschi M, Petretto A, Santucci L, Del Boccio P, et al. Repetitive fragmentation products of albumin and alpha1-antitrypsin in glomerular diseases associated with nephrotic syndrome. J Am SocNephrol. 2006;17(11):3139-48.