Review Article

Urinalysis – A Simple Diagnostic Tool In Kidney Disease

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Abstract

Urine is a window to understand diseases of the kidney. The product of kidney the urine is freely available and can be easily collected non-invasively. Urine microscopy dates back its origin in 1830 and still remains an important tool to physician. Urinalysis is much more than urine microscopy and it includes measurement of urine specific gravity,pH,estimation of solutes like protein,glucose etc.In the era of modern medicine, urinalysis is a powerful tool in diagnosing the etiology and prognosticating diseases of kidney and urinary tract.This article discusses the parameters in urinalysis and its usefulness in diagnosing diseases of kidney and urinary tract.

Key Words: Urinalysis, Hematuria, Proteinuria, Urinary Cast, Glomerulonephritis, Chronic Kidney Disease.

Introduction

Clinical Urine Microscopy dates back its origin in 1830 and it was first done by Rayer et al in Paris.[1] Since then it is an important basic diagnostic test in clinical practice. Urinalysis includes estimating physical characteristics of urine like color, clarity, specific gravity and its chemical characteristics like pH, presence of hemoglobin, protein, glucose, ketones, urobilinogen, bilirubin, leucocytes, esterase,nitrates and urine microscopy for urine sediments.

Procedure of Urine Collection

Results of urinalysis are greatly influenced by the way and accuracy with which it is being collected and handled in laboratory. Patients are advised to avoid strenuous exercise 72 hours prior to sample collection to avoid exercise induced proteinuria and hematuria.[2] Women are advised to avoid sample collection during menstruation. First or second voided early morning urine sample is preferred.

Though supra-pubic aspirations yield the best sample with minimal chances of contamination[3], most physicians prefer freshly voided sample. Contamination while sample collection occurs more likely in women than men and the most important step to obtain a clean catch sample is to hold the labia wide apart during voiding.[4] The classic clean catch mid-stream technique involves holding the labia wide apart, cleaning the perineum, and collecting midstream urine. Men should be asked to retract the prepuce before sample collection. Several studies showed that cleaning the perineum made little difference in contamination rate.[5,6]

There should not be excessive time lag between collection and examination of sample. It is advisable to refrigerate urine, as delay of more than 2 hours can give unreliable results.[6]

Physical Characteristics

Appearance

Naked eye appearance of urine to diagnose physical conditions is being used from Stone age.[1] Freshly voided urine is normally clear and transparent. It may be yellow to deep yellow depending on the hydration status of the patient. To the experienced person, the appearance of urine itself will provide important diagnostic clues. (Table 1)

Color of urine	Possible diagnosis
Cloudy or turbid urine	Urinary tract infection Contamination from genital secretions
Cola colored urine	Post-streptococcal glomerulonephritis
Red urine	Gross hematuria Hemoglobinuria Myoglobinuria
Milky White urine	Chyluria
Pink urine	Uric acid crystalluria
Velvet urine	Ecoli UTI
Frothy urine	Heavy proteinuria

Table1: Clinical clues obtained from the color of urine specimen

Age of the patient is very important in analyzing the results for eg:Painless hematuria in elderly patient should prompt evaluation for urinary tract malignancy whereas syn-pharyngitic hematuria in a child is suggestive of IgA Nephropathy.[7]

Odour

Normal Urine have mild smell termed as urinoid.[6] Dehydration can impart strong ammonia odour to urine. Bacterial infection of urine leads to excess ammonia production and imparts offensive or pungent odor to urine. Fecal smell of urine is seen in gastrointestinal bladder fistulas.[6]

Concentration Of Urine

It is measured by a number of methods, commonly used being specific gravity, osmolality, refractometry. Specific gravity of urine is determined by its solute concentration. It measures the ability of kidney to concentrate urine. Gold standard method for determining specific gravity is using a urinometer.[8] Urinometer is actually is a hydrometer, which has a weighted float and thin stem with graduations from 1.000 to 1.060 that sinks in the test liquid to a depth directly proportional to the specific gravity of the liquid. Since it needs large amount of urine sample and is cumbersome, it is largely replaced by newer methods. Nowadays specific gravity is determined by dry chemistry incorporated into urine dipsticks.[8] Dipsticks underestimate specific gravity whenever urine pH is less than 6.5 and overestimates specific gravity whenever there is protein, glucose, or urea is present.[8] Studies have shown that dipstick method does not correlate accurately with the results obtained by osmolality and refractometry.[9]

Normal urine specific gravity ranges from 1.002 to 1.030.[10] Hyposthenuriais seen in diabetes insipidus, glomerulonephritis, pyelonephritis, diuretic use, aldosteronism - due to loss of renal tubular concentrating ability. Increased urine specific gravity is seen in dehydration, Syndrome of inappropriate ADH secretion (SIADH), or following contrast agent. Specific gravity of 1.010 - isosthenuria - is seen in conditions with impaired urinary concentration for eg: acute tubular necrosis and chronic kidney disease ; 1.010 being the specific gravity of the glomerular filtrate.

Refractometry is now preferred because of its simplicity and the need for only a single drop of urine.[8] It is based on the measurement of refractive index which in turn depends on the solute properties. It shows false results in presence of protein, glucose and contrast dye as they have high molecular masses compared to normal components of urine so in such situations urine osmolality measurement with osmometer is preferred.[6]

Osmolality is measured by an osmometer and is not influenced by urine temperature and protein concentration[6]. However high glucose in urine will cause increased osmolality.

Chemical Characteristics

pH

Normal urine is slightly acidic though it can range from 4.5 to 8. Urine pH usually corresponds to serum pH except in patients with diseases like renal tubular acidosis(RTA).Hallmark of RTA is the inability to acidify urine to pH less than 5.5 despite acid loading and overnight fasting.[6] It is measured using dipsticks, which can detect pH from 5 to 8.5. It cannot detect accurately when pH is less than 5.5 or more than 7.5. Whenever accurate measurement of urine pH is needed pH meter with glass electrode is preferred.[8]

Urine pH is low in metabolic acidosis, with high protein meals due to more ammonia production, volume depletion.[4] Studies suggest that low urine pH herald onset of reno-vascular disorder in diabetes. Metabolic acidosis and low urine pH is associated with worsening of renal parameters in CKD and many complications in CKD; thus enforcing the need for early initiation of alkalinizing agents in CKD.[11]

High urine pH is seen in renal tubular acidosis - distal RTA, vegetarian diet , infection with urease producing organism such as Proteus that generate NH_3 from urea.[4] pH determination of urine is useful in the diagnosis and management of urinary calculi.[12] Alkaline urine in a patient with calculi suggests the presence of urea splitting organism which is associated with magnesium ammonium phosphate crystals and staghorn calculi whereas acidic urine is associated with uric acid stones. Alkaline urine also favours formation of calcium phosphate stones.[12]

Hemoglobin

It is detected with the help of urine dipsticks which detects pigments in urine sample – either hemoglobin or myoglobin.[4] This cannot differentiate hematuria from hemoglobinuria, so urine microscopy is essential.[13]

Protein

Proteinuria - the hallmark of kidney disease - is defined as urine protein excretion of more than 150mg per day.[14] Mechanism of proteinuria may be glomerular, tubular or overflow.[6] Glomerular proteinuria is principally albumin whereas tubular proteinuria includes low molecular weight proteins other than albumin which are no longer metabolized or reabsorbed by the malfunctioning tubules. Overflow proteinuria occurs when there is too much low molecular weight proteins exceeding the reabsorptive capacity of the tubules.[6] Proteinuria can be quantified using different methods namely

1. Dipstick method
2. 24 hour urine protein excretion
3. Protein creatinine ratio.[4]

Dipsticks are now dominating rapid diagnostics because of its low cost and ease.[15] This method is highly sensitive for albumin and allows a semi - quantitative estimation of protein, but has low sensitivity for other proteins and hence it may not detect tubular proteinuria. The major disadvantages of dipstick are its variable sensitivity, inability to detect tubular proteinuria and marked operator dependency. Sensitivity and specificity of dipstick largely depends on the concentration of albumin which in turn will be greatly influenced by the volume and concentration of urine.[15] Since it is inexpensive, it can be used as an effective screening tool to identify renal disease in general population. 24 hour urine protein estimation is the gold standard method for estimating proteinuria.[4] It takes into account the circadian variation in proteinuria, but it is less practical to perform in outpatients. This method may not be accurate due to incomplete collection of sample, variable diet, activity and hydration status of the patient.[4]

Studies support Urine spot Protein /Creatinine ratio as an acceptable alternative to 24-hour urine protein estimation and spot value is not influenced by hydration and diuresis.[4] A normal spot PCR rules out proteinuria but an elevated spot PCR should always be confirmed by a 24 hour estimation. PCR is not considered reliable for follow up of patients with proteinuria .

Several CKD management guidelines including Kidney disease improving Global outcomes (KDIGO) and UK National Institute for Health and Clinical Excellence (NICE) recommend urine albumin creatinine ratio (uACR) to PCR in quantifying proteinuria . Urine PCR is more sensitive than ACR and both are equally good in predicting adverse clinical outcomes.[16] Assessment of both albuminuria and non-albumin proteinuria(NAP) aids in diagnosis and prognosis as albuminuria reflects glomerular injury and non-albumin proteinuria indicates tubulointerstitial pathology.

Urine protein excretion follows a circadian pattern and hence it tends to be highest in the afternoon, uACR tends to be most accurate when done on the first voided, early morning sample. Studies have shown that ACR doesn't vary with urine concentration as albuminuria is being corrected for creatininuria.[16] Guidelines suggest first morning uACR as the preferred method for assessing albuminuria in diabetic as well as non-diabetic individuals.[16]

Qualitative assessment of protein is done by urine protein electrophoresis, SDS PAGE (Sodium dodecyl sulfate -polyacrylamide gel electrophoresis) can be used to differentiate the proteins based on their molecular weight.[4] In some patients the detection of a single protein may be diagnostic eg: Neutrophil Gelatinase associated Lipocalin (NGAL) as an early predictor in acute kidney injury and Bence Jones proteinuria in multiple myeloma.[4]

Urine Biochemistry In Infection

Leucocyte Esterase

Leucocyte esterase is the enzyme produced by neutrophils and macrophages and is seen in urinary tract infection.[4] It is detected with a dipstick which measures indoxyl esterase activity from lysed neutrophils and macrophages. So it will be positive even when urine microscopy is negative. False positive results may occur due to contamination from bacteria in vaginal secretions. Leucocyte esterase has a low sensitivity, specificity, positive predictive value but a very high negative predictive value in diagnosing UTI and hence can be used as an effective screening test for urinary tract infections.[17]

Nitrites

Nitrites dipstick test helps in diagnosing UTI by bacteria that reduce nitrates to nitrites. This include most gram negative uropathogenic Enterobactericeae.[4] Pseudomonas, Enterococcus and Staphylococcus albus-which are also common uropathogens, cannot be detected by this test due to their lack of ability to convert nitrate to nitrite.[4] Sensitivity of the test is very low and it requires the patient to be on a nitrate rich diet, which forms the substrate of the test. It requires sufficient holding time within the bladder as more than 4 hours is needed for the bacteria to convert nitrate to nitrite - hence can be done only on a first voided early morning sample.[6]

Microscopic Analysis

First or second voided early morning urine sample is preferred, the specimen should be promptly centrifuged, and sediment subjected for microscopy.[4] Urine pH and specific gravity are necessary information for microscopy as high pH favors lysis of erythrocytes and leucocytes and impairs cast formation and precipitates phosphates.[4]

Phase contrast microscopy is preferred over bright field microscopy and polarized light is used to characterize lipids and crystals.[4] At least 10 fields should be examined in low and high power field before reaching conclusion.

Cells

Urine microscopy is essential in differentiating hematuria from hemoglobinuria. American Urological association defines hematuria "as the presence of 3 or more RBCs per high powerfield in 2-3 urine samples".[6] Glomerular hematuria[4] is found to be present when there is dysmorphic RBC's contributing more than 80% of the total erythrocytes with significant proteinuria and RBC casts. Non-glomerular hematuria has isomorphic RBCs and insignificant proteinuria and is secondary to tubulointerstitial, reno-vascular or metabolic causes. Urologic hematuria is distinguished from the other two by the absence of RBC casts, proteinuria and dysmorphic RBC.[6,8]

Leucocytes in urine signify lower or upper UTI though upto 3 leucocytes /HPF in men and upto 5 leucocytes /HPF in women are considered normal. Neutrophils may also be present in upper or lower urinary tract infection or acute or chronic interstitial nephritis or proliferative or cresentic glomerulo nephritis.[4] Eosinophiluria indicate acute allergic interstitial nephritis and may also be seen in chronic pyelonephritis, cholesterol embolism, urinary schistosomiasis and prostatitis.[4] Presence of lymphocytes in urine in a post-transplant patient may be indicative of acute cellular rejection.[8]

Macrophages engorged with lipid droplets are seen as 'oval fat bodies' in nephrotic syndrome.[4] Macrophages in urine are also seen in active glomerulonephritis like IgA nephropathy.[18]

Renal tubular epithelial cells are a marker of tubular damage and are found in acute kidney injury, acute interstitial nephritis, and acute cellular rejection of a renal allograft. Damaged and necrotic tubular epithelial cells are seen in AKI and in glomerular disorders they have a normal appearance.

Superficial cells of uro-epithelium is a common finding but cells from the deeper layers indicate severe damage secondary to stones, malignancy or urethral stents.[4] Lipids in urine may be seen as free lipids or as oval fat bodies or as fatty casts or as cholesterol crystals. Lipids are typically seen in glomerular diseases with proteinuria.

Casts

Casts are formed in the lumen of distal renal tubules and collecting ducts and their matrix is formed by Uromodulin or Tamm-Horsfall glycoprotein.[4] Trapping of cells within the matrix produces specific types of casts. (Table :2)

Cast	Associated conditions
Hyaline	normal ,renal disease
Hyaline - granular	Normal ,renal disease
Granular	Renal disease
Waxy	Renal disease, Rapidly progressive renal disease
Fatty	Marked proteinuria, nephrotic syndrome
Erythrocyte	Glomerular hematuria Necrotizing or proliferative glomerulonephritis
Hemoglobin	Glomerular hematuria Necrotizing or proliferative glomerulonephritis Intra vascular hemolysis
Leucocyte	Acute interstitial nephritis Acute pyelonephritis Proliferative glomerulonephritis
Renal tubular epithelial cells	Acute tubular necrosis Acute interstitial nephritis Nephrotic syndrome Proliferative glomerulonephritis
Myoglobin	Rhabdomyolysis

Table 2: Types of casts and the conditions associated

Crystals[4]

A thorough knowledge of crystal morphology is essential for the correct identification of crystals. Crystals in urine, aids in the diagnosis and assessment of patients with stone disease and in suspected drug nephrotoxicity. Uric acid crystals are amber colored rhomboid or barrel shaped crystals seen in acidic urine, which are polychromatic under polarizing microscopy. Large numbers of uric acid crystals are seen in acute urate nephropathy. Calcium oxalate crystals are either ovoid (mono hydrated) or bipyramidal (bihydrated). Monohydrate polarizes light whereas bihydrate do not. Calcium phosphate crystals are pleomorphic and precipitate in alkaline urine and they polarize light intensely. Monohydrated calcium oxalate crystals are seen in AKI due to ethylene glycol intoxication.

Amorphous phosphates are often confused with amorphous uric acid but they do not polarize light. Triple phosphate crystals appear like coffin lids and are found in alkaline urine .They strongly polarize light and are indicative of UTI with a urease splitting organism. Cystine crystals precipitate in acidic urine, have hexagonal shape and their size predicts the recurrence of cysteine stones.[2,8] Dihydroxyadenine crystals are a marker of homozygotic deficiency of enzyme adenine phosphoribosyl transferase. These are brownish spherical crystals with radial striations from centre and they strongly polarize light. The affected people have crystalluria and have radioluscent renal stones, AKI or CKD.

Organisms

UTI is suspected whenever bacteria are seen in a freshly voided sample along with leucocytes.[6] Schistosoma hematobium may be seen in endemic areas, which is the culprit of recurrent hematuria and obstructive uropathy.[4]

Conclusion

Urinalysis is a basic investigation to assess the renal function and is correctly termed as "poor man's renal biopsy". It is a very easy and inexpensive investigation providing diagnostic and prognostic clues. In addition to the above said basic parameters there are many newer markers for acute kidney disease and renal malignancies and is ever-expanding.

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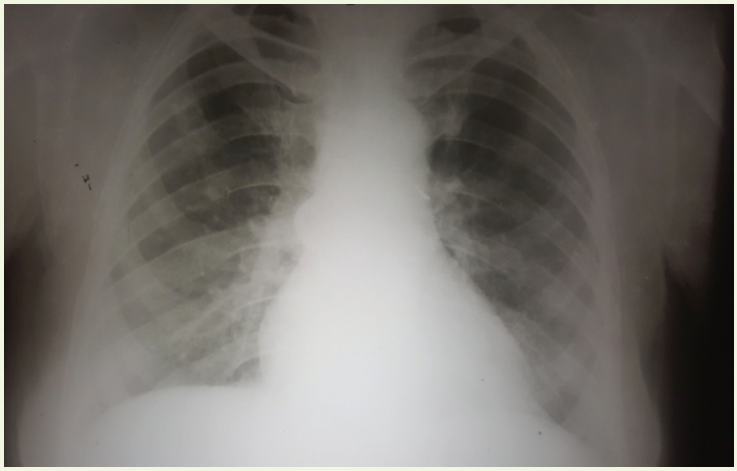
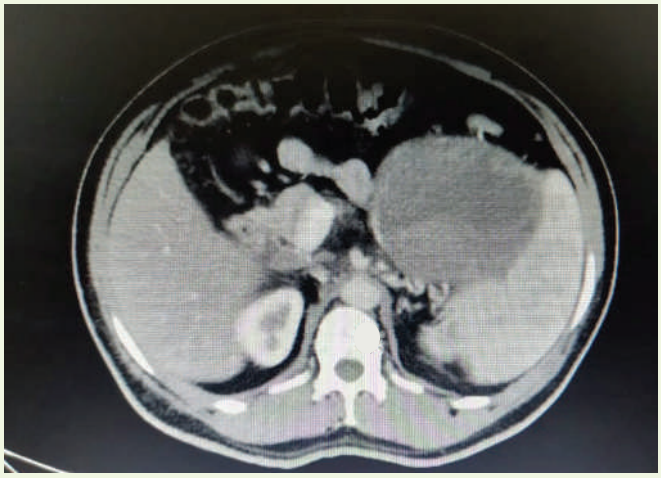
Image Challenge - 1



Clue:H/O Cough, weight loss, fever

- Answer in page : 62

Image Challenge - 2



Clue: H/O Loin pain, mass in flank

- Answer in page : 63