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Urinalysis in primary care doctor practice

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Abstract

Introduction:

A urinalysis is a simple diagnostic test which is used to detect wide range of disorders including urinary tract infections, kidney disease and diabetes. Moreover, it can be a useful tool to monitor a medical condition. A urine analysis might be a part of routine medical exam

in order to check patient's health condition but it is not recommended as a preventive screening test in the population. We believe that this article will contribute to spreading important knowledge especially in primary care.

Aim of the study:

The aim of the article is to collect and summarize basic information on urinalysis. We collected elemental information about routine urine examination, which includes assessment of physical properties, chemical properties and sediment composition. This knowledge is useful in the daily practice of a primary care doctor.

Material and methods:

Literature available in the PubMed database, ScienceDirect and ClinicalKey was reviewed using the following keywords: "Urinalysis"; "Urine sediment", "Urinary tract infection"

Conclusions:

The ability of proper urine analysis is crucial in clinical practice. Performing the test is technically simple and widely available. It is important to be aware of the limitations of urine analysis. Therefore if results of urinalysis is unusual, it is necessary to require more testing to find the source of the medical issue.

Keywords: "Urinalysis"; "Urine sediment"; "Urinary tract infection".

Introduction

A Urinalysis is a common laboratory test used in the clinical practice of primary health care. Although urinalysis is not recommended as a preventive screening test in the population, family doctors should have the knowledge and skills to interpret the urine test results. Urinary abnormalities identify high risk groups of patients including diabetes and hypertension. The routine urine examination consists of assessment of physical properties (color and transparency, specific gravity, pH), chemical properties (protein, glucose, hemoglobin, urobilinogen/bilirubin, ketone bodies) and sediment composition (leukocytes, erythrocytes, renal tubular epithelial cells, casts). Strip tests can be used to determine the presence of proteins, glucose, ketones, hemoglobin, bilirubin, urobilinogen, acetone, nitrite and

leukocytes, as well as pH and specific gravity (1). A Urinalysis can be problematic due to the occurrence of false positive and false negative results. Therefore, we should be aware of the limitations of urinalysis and consider the patient's clinical condition and the results of other additional tests. Patients usually collect their own urine sample, so it is crucial to tell them exactly how to do it correctly. Midstream method is comparable to the results obtained by bladder catheterization and is much less invasive (2). Illustrated information materials may reduce the risk of sample contamination with bacterial flora (3). This test has no contraindications, although it should not be performed during menstruation due to the high risk of contamination of the sample with red blood cells (4). The aim of the article is to collect and summarize basic information on urinalysis, the knowledge which is necessary in the daily practice of a family doctor.

Technique

Proper instruction and correct urine collection are crucial elements to obtain a reliable result, which is necessary to make an accurate diagnosis. The apparent ease and obviousness of sample collection carries the risk of pre-laboratory error, which can decrease the diagnostic value of the test. Reducing the number of false-positive cultures can be achieved by implementing simple hygiene rules also antiseptics should not be used because they reduce the growth of microorganisms in the urine sample (5).

In practice, the morning sample taken from a mid-stream is the preferred, because it is less contaminated by epithelial cells and microorganisms. Urine samples should be collected in disposable, sterile, tightly closed packages with a capacity of at least 50 ml. The collected urine should be sent to the laboratory after approximately 2 hours. (6), Exceeding that time could disturb the composition of urine components and make the result non-diagnostic (7). If this is not possible, use preservatives or store the sample in a refrigerator at 4 degrees Celsius, because refrigeration reduces the growth and metabolism of bacteria. A urine culture sample can be kept in the refrigerator for a maximum of 24 hours (6). Urine analysis using test strips is a convenient and quick method, but it may result in false-positive and false-negative results. Despite their economic benefits, they are less accurate than laboratory measurements and should not be used for quantitative measurements of albuminuria or proteinuria (8).

Patient education should include explanation of technical aspects of urine collection and emphasize the effects of possible confounding factors such as diet and exercise. Family doctors should take into consideration these aspects and clarify the facts to the patient. That enables draw correct conclusions from the urine analysis.

Urine analysis

Color and transparency

The color of physiological urine ranges from practically colorless to dark yellow (amber) depending on the concentration of urochrome (9,10). Abnormal changes in urine color may be caused by pathological conditions, medications or food. Probable causes of the color change are summarized in the table below based on (11,12). The most common abnormal urine color is red or reddish-brown. Menstrual blood can commonly be a potential source of red discoloration of urine sample. Hematuria, hemoglobinuria and myoglobinuria may cause pink, red or reddish-brown discoloration(1). Physiological urine is clear, therefore, when turbidity is observed, differential diagnosis is essential. Phosphate salts may precipitate in the form of crystals, especially in alkaline environment and dissolve again after adding acetic acid (9). The presence of leukocytes or bacteria in urine may cause changes in clarity similar to phosphates, but the turbidity does not disappear after the urine sample is acidified. Prostatic fluid, semen, mucus from the genital tract and contamination with some antiseptics can cause urine turbidness (1). A rare cause of turbidness is chyluria, a condition in which urine contains lymph due to obstruction of lymph flow or rupture of lymphatic vessels. A change in the color of urine is often noticed by patients and dispose to make a doctor's appointment.

Table.1 Urine discoloration – possible causes

Color	Possible cause
Red	Menstrual contamination; food - beetroot, blackberries, rhubarb; drugs - Rifampicin; Pathological conditions - hematuria in the course of acute kidney injury, rhabdomyolysis, porphyria.
Black	Food - Cascara Sagrada; methyldopa, levodopa; pathological conditions - phenol poisoning, methemoglobinemia, excess melanin in the course of metastatic melanoma; iron sulfate supplementation, alcaptonuria
Orange	Drugs – fenotiazins, rifampicin, sulfasalazine; bile pigment, uricosuria.
Yellow	Food - carrot, Cascara; concentrated urine; bile pigment.
Green and blue	Food - asparagus, spinach; drugs - amitriptyline, cimetidine, promethazine, triamterene; pathological conditions - urinary tract infection (UTI) caused by Pseudomonas aeruginosa infection; biliverdin, methylene blue.
Brown	Food - broad beans; drugs - levodopa, metronidazole, nitrofurantoin, antimalarial drugs, sulfonamides; Addison's disease.
White	Chyluria, Pyuria, Lipiduria Hypercalciuria, Hyperoxaluria, Phosphaturia

Urine specific gravity

The specific gravity of urine is a amount of osmotically active particles dissolved in the urine. It is assumed that the norm for a healthy person under 60 years of age should range from 1.023 to 1.035 and >1.021 in older people. To determine the specific gravity, the sample should be taken after abstaining from fluids for at least 8 hours. The relative density of urine is an important parameter. It reflects especially the kidneys excretory efficiency and ability to save water. A specific gravity greater than 1.035 always indicates the presence of non-physiological components in urine (glucose, protein, contrast agent) as well as dehydration, excessive fluid loss (vomiting, diarrhea, fever), diabetes, congestive heart failure, syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and adrenal insufficiency (9). Relative urine density below 1.004 is characteristic for complete deficiency of antidiuretic hormone, central or nephrogenic diabetes insipidus, kidney damage in the course of glomerulonephritis, pyelonephritis and excessive fluid intake (13). Isosthenuria refers to the relative density of urine at the level of 1.010-1.012. It reflects decreased kidney function and a significant reduction in the number of functional nephron. The result is the inability to concentrate and dilute urine (14).

pH

The pH value of urine is between 4.5 and 8.0. The pH of a healthy person's urine should be slightly acidic in the range of 5.0-6.0. pH is measured by test strips. The pH value of urine in most cases reflects the acid-base balance of the body. Low urine pH is observed in the course of metabolic acidosis, consumption of high-protein meals (they generate large amounts of H^+ and NH_4^+ ions) and loss of circulating volume (the effect of H^+ ion secretion as a result of the compensatory effect of aldosterone). High urine pH values are observed in the case of vegetarian diets, especially vegetables and citrus fruits (a minimal amount of H^+ and NH_4^+ ions are generated) and infections of the urinary tract with urease-positive microorganisms (10,15).

Protein

Proteinuria is the earliest marker of nephrons damage. The correct amount of protein in urine should not exceed 150 miligrams per day. Albumin should constitute approximately 30 mg (16). The presence of protein in urine may indicate various abnormalities. We are able to determine proteinuria based on 3 available tests. Test strips detect changes in pH depending

on the amount of albumin in the urine. Low specific gravity of urine or proteinuria can give false negative results. Alkaline urine can give false positive results. 24-hour measurement of proteinuria is gold standard method for detection of proteinuria, especially when it comes to monitoring treatment. 24-hour urine protein measurement has some limitation. It can be performed during hospitalization and it is impractical in some groups (children and the elderly). The last test, both easily available and alternative to 24-hour proteinuria measurement, are the protein-to-creatinine ratio and albumin-to-creatinine ratio. In the case of older people, the measurement of albumin-to-creatinine is recommended as a good indicator of the progression of chronic kidney disease. Protein-to-creatinine ratio detect proteinuria resulting from tubular damage or monoclonal gammopathies in children population (10).

There are several types of proteinuria. Accidental detection of proteinuria may be a temporary condition associated with high fever, dehydration, physical exercise and exposure to cold. Proteinuria has no clinical significance in these cases. Orthostatic proteinuria is a benign type of proteinuria seen mostly in children and young adults. Upright position can be associated with the presence of protein in the urine. Proteinuria should be confirmed in two urine samples. The first one in the morning right after waking up and the next one after a few hours. The absence of proteinuria in the first sample and the presence of proteinuria in the second sample allows us to confirm the presence of orthostatic proteinuria (6,16).

Glomerular proteinuria is associated with damage to the glomerular barrier and is characterized by a protein loss of more than 1 g/day (17). Glomerular barrier can be damaged by toxic substances and immune complexes in the course of systemic lupus and streptococcal glomerulonephritis. Tubular proteinuria is associated with the presence of low molecular weight proteins in urine, which indicates damage to the proximal tubule. Tubule contours can be damaged by exposure to heavy metals and toxic substances. It also occurs in the course of acute viral infections and as a component of Fanconi syndrome. Compared to glomerular proteinuria, which can reach up to 4 g/day, proteinuria due to tubular damage has no clinical significance. Prerenal proteinuria is associated with the presence of high concentrations of low-molecular-weight proteins in the blood, such as hemoglobin, myoglobin or acute phase proteins. High amount of proteins exceed the renal threshold for protein reabsorption. Multiple myeloma cause prerenal proteinuria, which results in excessive secretion of monoclonal proteins into the urine. Post-renal proteinuria is usually characterized by a small amount of protein in the urine. Common conditions can be associated with post-renal

proteinuria for example UTI and nephrolithiasis (6) . Albuminuria is a very sensitive indicator in the course of diabetic kidney disease. It is possible to predict long-term renal complications such as chronic kidney disease, cardiovascular diseases and increased overall mortality (10).

Glucose

Glucose is filtered in the renal glomeruli and completely reabsorbed in the proximal tubule. The renal threshold for glucose is approximately 190 mg/dL. If threshold is exceed glucose can be detected in the urine sample (18). Glucose may appear in urine in patient with diabetes mellitus. Glucosuria can be a manifestation many disorders for example: Cushing's syndrome, acromegaly, hyperthyroidism, pheochromocytoma [19], pancreatitis, pancreatic cancer, glycogen storage disease, obesity, burns, infection, fractures, myocardial infarction and Fanconi syndrome (1,19,20). It is worth adding that glucosuria may be side effect of flozins (21). False-negative glucose results occur in the presence of ascorbic acid and bacteriuria. False-positive results can be observed in the presence of detergents and a high acid urine pH (10).

Ketone bodies

Ketone bodies should not be present in a urine sample. The detection of ketonuria does not have to be caused by type 1 and type 2 diabetes. It may be result of hypercatabolism, starvation, persistent vomiting, excessive alcohol consumption, malabsorption syndromes and psychiatric eating disorders such as anorexia or bulimia. Incorrect administration of insulin can result with ketonuria in a patients with diabetes mellitus (6).

Bilirubin/urobilinogen

In a normal physiological state, bilirubin is not detectable in the urine. Bilirubin may be found in urine conjugated with glucuronic acid in some diseases. That water-soluble complex is able to pass through the filtration barrier of the glomerulus. Bilirubinuria occurs in parenchymal and obstructive jaundice. We are able to determine it in a urine sample much earlier than we can observe clinical jaundice. Physiologically, conjugated bilirubin is secreted into bile and then broken down into bile acids and urobilinogen. Small urobilinogen fraction is absorbed from the colon and if it is not taken up on the first-pass effect in the liver, it enters directly the circulation. In the case of diseases such as hepatitis B and C, liver cirrhosis and drug-induced

liver damage, we observe an increased level of free bilirubin in the form of the metabolite urobilinogen (15).

URINE SEDIMENT

ERYTHROCYTURIA

Hematuria is defined as the presence of an abnormal number of red blood cells in the urine (three or more red blood cells in the visual field) (20). Clinically, we deal with microscopic hematuria - microhematuria and macroscopic hematuria (macrohematuria) (9). Excessive erythrocyte excretion change the color of the urine sample visually and it is called macroscopic hematuria (22). 0.5 to 1.0 militer of blood in 1 liter of urine is enough to cause a color change (9). Microhematuria is defined as as 3 red blood cells per high power field on microscopic evaluation (23). The presence of hematuria may be associated with urinary system diseases such as acute and chronic glomerulonephritis, drugs, toxins or immunological disorders. Acute tubular necrosis, urinary tract neoplasia, cystitis, kidney injure or viral infection can also present as hematuria. Increased number of erythrocytes in the urine combined with erythrocyte casts can indicate renal origin (1). Pseudo-hematuria is an accidental contamination of sample (9). A relatively common phenomenon is hematuria caused by intense physical exercise for example long-distance running. After 48-72 hours the repeated results of urine should be normal (24).

LEUCOCYTURIA

The presence of more than 3 leukocytes in the visual high power field or $>10/\text{mm}^3$ of microorganisms in urine is called pyuria (25). In clinical practice, the observed number of leukocytes in the visual field of up to 5 or more in women is still considered as norm and does not indicate any abnormalities (1). Turbidity, color change and specific smell of urine caused by the presence of leukocytes and microorganisms do not allow us to recognize pyuria; the diagnosis requires microscopic confirmation (9). The main cause of increased leukocyturia are bacterial infections of both the upper and lower urinary tract. Less frequently parasitic and viral infections. An increased number of leukocytes in urine is also observed in the course of

glomerulonephritis, tubulointerstitial nephritis, systemic lupus and cholecystitis in the course of urolithiasis. Leukocyturia may temporarily persist during fever and intense exercise (1).

Casts

Casts are a well-known component of urine sediment. They constitute a cast of the lumen of the renal tubule and consist of proteins, fats, erythrocytes and other cellular elements. There are some most important casts from a clinical point of view. Erythrocyte casts are defined as combined normal or damaged erythrocytes in the lumen of the renal tubule. They very often appear in the case of damage to the renal tubular epithelium and excessive anticoagulation. They may indicate glomerulonephritis, hematuria of renal origin and rare warfarin nephropathy. Leukocyte casts are present in the sediment in cases of pyelonephritis. The main etiology of ascending pyelonephritis is *Escherichia Coli* infection. Less common cause is hematogenous dissemination of *Staphylococcus* and *Streptococcus* species. Leukocyte casts are not only correlated with bacterial infections but also in the course of a rapidly progressive glomerulonephritis, viral and fungal infections (26). Hyaline casts are the most common type of casts and consist Tamm-Horsfall protein. An increased number of hyaline casts in the sediment occurs transiently during: physical exercise, exposure to heat, dehydration, fever, congestive heart failure and diuretic treatment (1). Their presence in urine has no significant diagnostic significance (9). Granular casts occur in the course of tubulointerstitial inflammation, glomerulonephritis, tubular damage and kidney transplant rejection. They may also occur with other casts in the course of pyelonephritis and viral infections. Intensive physical training session and stressful life event experience can also be associated with granular casts in the sediment (1). Waxy casts are formed during chronic inflammatory and degenerative processes of renal tubule cells. Their presence in urine sediment may indicate acute glomerulonephritis, acute renal necrosis and end-stage renal failure. The presence of wax casts always indicates serious kidney damage (1,9). Fatty casts occur mainly in patients with massive proteinuria. Epithelial casts occur in acute renal tubular necrosis caused by cytomegalovirus infection and exposure to certain drugs (1).

URINE CULTURE

Urinary tract is sterile, except for the final part of the urethra, where microorganisms are found. For this reason, the urine of a healthy person may contain a small number of microorganisms, the number of which does not exceed 10,000 in 1 milliter of freshly passed urine (9). Significant bacteriuria is the finding of bacteria in a urine sample $10^3 - 10^5$ Colony Forming Unit(CFU) per milliter. The sample should be obtained in a way that minimized contamination. The definition of significant bacteriuria is summarized in Table 2 (27). Cystitis most often manifests itself by increased pressure on the bladder, dysuria, frequent urination, microscopic hematuria and less frequently abundant hematuria and suprapubic pain (28). Untreated infections may lead to pyelonephritis, which is associated with fever, nausea, vomiting and flank pain. Pyelonephritis carries an increased risk of sepsis. If symptoms of UTI and significant bacteriuria occur, antibiotic therapy is recommended (29). Asymptomatic bacteriuria is a condition in which there is significant bacteriuria without the presence of UTI symptoms. Asymptomatic bacteriuria is a common phenomenon occurring in some populations and does not require antibiotic therapy, except for pregnant women, individuals undergoing endourological procedures associated with mucosal trauma and patients undergoing transurethral resection of the prostate (30)

UTI may be caused by many species of bacteria and fungi. The majority of UTI is caused by *Escherichia coli*, especially Uropathogenic *Escherichia Coli* (UPEC) (31). UTI can be classified as complicated and uncomplicated. Uncomplicated UTI affects healthy people without structural or neurological disorders in the urinary system (32). UPEC is the most common cause of both complicated and uncomplicated UTI. Other microorganisms causing uncomplicated UTIs are *Klebsiella pneumoniae*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, Group B *Streptococcus*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida* species. Complicated UTI are caused by *Enterococcus* species, *Klebsiella pneumoniae*, *Candida* species., *Staphylococcus aureus*, *Proteus mirabilis* and *Pseudomonas aeruginosa* (31). Absence of significant bacteriuria does not rule out UTI. Sterile pyuria is the presence of white cells in the urine in the absence of bacteria. Such a situation may raise the suspicion of infection with other microorganisms such as *Bacillus Tuberculosis*, atypical bacteria, anaerobic bacteria, fungi, viruses and parasites. Analgesic nephropathy and interstitial nephritis can manifest as sterile pyuria (33). Bacteriuria can be detected by testing a urine sample with a dipstick test for nitrites because many species of bacteria that cause UTIs have the ability to reduce nitrates to nitrites (1). Leukocyte esterase is an enzyme produced by neutrophils and may be a sign of UTI-related pyuria. Negative results of nitrite

concentration and leukocyte esterase activity in urine allow to exclude infection, while positive results must be confirmed by positive finding of urine culture or clinical symptoms (34). Nonpregnant women with a first uncomplicated UTI are not obliged to collect midstream urine sample. In such a situation, positive test strip results for the presence of nitrites and leukocyte esterase in urine and the presence of clinical symptoms in the urinary system are sufficient to confirm a urinary tract infection (35). Strip tests enable to quickly confirm or exclude of UTI and do not require laboratory facilities.

Table 2. Determination of significant bacteriuria from a single midstream sample from a man or woman

Clinically symptomatic UTI in non-catheterized patients	$\geq 10^3$ CFU/mL
Clinically asymptomatic UTI in non-catheterized patients	$\geq 10^5$ CFU/mL*
Clinically symptomatic UTI in catheterized patients	$\geq 10^3$ CFU/mL
Clinically asymptomatic UTI in non-catheterized patients	$\geq 10^5$ CFU/mL

* in the case of women, two urine cultures taken from the midstream are necessary,

Conclusion

Urine analysis interpretation is crucial in clinical practice. Urine analysis can provide information about functional and structural disease processes in the urinary system (1) . Performing the test is technically simple and widely available. Doctors should be aware of its limitations and take into account possible interfering factors such as a vegetarian or high-protein diet, excessive fluid intake or the state after intense physical exercise. First morning midstream sample ensure the detection of substances that may not be present in a diluted random sample. Patients most often collect urine samples themselves, so possible pre-

laboratory errors should be taken into account. In a family doctor practice, strip tests are a quick and useful method for excluding urinary tract infections. Quick strip tests are not indicated for quantitative measurements of albuminuria or proteinuria. If we suspect hematuria of glomerular origin of disease due to the presence of proteinuria, erythrocytic casts or increased creatinine levels in the blood, we should refer patient to the nephrology clinic. Erythrocytes presence can be correlated with urinary tract disease (36). Urine analysis is a useful tool for diagnosing urinary and systemic diseases.

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Conflicts of Interest

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