The Urinalysis—Inexpensive and Informative

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The urinalysis dates back 6000 years. Information has evolved from tasting it for sugar to computer assisted assessment for the presence of cells and casts. The urine gives valuable information about kidney function in general and the glomeruli in particular. Findings can lead to a diagnosis of various medical conditions, most notable being diabetes mellitus. Proteinuria has many implications, including the presence of systemic disease and the progression of an underlying renal condition.

The Babylonians were the first to study urine 6000 years ago. Then Hippocrates studied the color and appearance of urine and was said to use the information to make medical diagnoses and even prognosticate based on this limited information. Questionable improvement in this prognostication was made by the “pisse prophets” in medieval times. The 18th and 19th centuries saw the dawn of chemical and microscopic analysis. Richard Bright was a strong believer in the importance of urinalysis, and at one time all kidney disease was referred to as “Bright’s Disease.” Robert Boyle discovered litmus paper in 1670 and with it the testing of pH. Mauments described the testing of urine for glucose in 1850, but the modern chemistry strips did not appear until 1956.1

The ideal specimen is a clean caught, first voided specimen that is collected midstream to avoid urethral contamination and examined within a matter of hours. The urinalysis contains a large amount of information that will be discussed below.

COLOR

- Cloudy—phosphates, urates, and leukocytes with bacteria
- Black—melanin, alkaptonurea, metronidazole, methyl dopa or carbidopa
- Brown to Red2—myoglobin, blood, free hemoglobin, beets, phenothiazines, phenolphthalein
- Orange to Yellow—bile pigment
- Green—pseudomonas, elavil (amitryptiline)
- Foamy—pyridium, proteinuria, conjugated bilirubin

pH

The normal pH is 4.5–7.8. An alkaline urine with a pH >7 is indicative of infection with a urea splitting organism, diuretic usage, vomiting, renal tubular acidosis, and respiratory diseases with hyperventilation.

An acid urine with a pH <5 is seen with acidosis, diarrhea, uncontrolled diabetes mel-
litus, starvation and dehydration, and respiratory diseases with CO₂ retention.

**SPECIFIC GRAVITY**

The normal specific gravity (SG) is 1.008–1.030, and it declines with advancing age reflecting the decreased ability of the kidney to concentrate the urine. The number and the weight of solutes affect it. By contrast, osmolality is determined solely by the number of solutes. As such, glucose and intravenous contrast materials raise the specific gravity much more than the osmolality. Hyposthenuria refers to a SG <1.007 and is seen in diabetes insipidus or fluid loading. Isosthenuria is a fixed SG of 1.010 and is seen frequently in glomerular and tubular disease and especially in renal failure.

**LEUKOCYTE ESTERASE AND NITRITES**

Esterase is released by lysed urine granulocytes. It is usually positive when there are more than 5 leukocytes per high power field. When compared to microscopy the esterase test has a sensitivity of 80% and a specificity of 70% for the presence of infection.

Most bacteria that colonize in the urine cause nitrates, which are derived from dietary metabolites, to be converted to nitrites.

When both tests are positive, it is highly likely that an infection is present.

**GLUCOSE AND KETONES**

A positive dipstick for glucose generally occurs when the plasma level exceeds 180 mg/dL. Exceptions are renal glycosuria from a defect in the function of the proximal tubule and occasionally in pregnancy when the threshold is lower. Glycosuria has a specificity of 98% but a sensitivity of only 17% and so is not useful as a screening test for diabetes mellitus. False negatives can be found in individuals on tetracycline and high dose vitamin C.

Ketones are generally detected with the nitroprusside reaction. They are commonly seen in fasting and starvation. Large amounts are seen in diabetic and alcoholic ketoacidosis and in aspirin poisoning. False positive results can be seen with ascorbic acid and from L-DOPA metabolites.

**PROTEINURIA**

The normal excretion rate of protein is 150 mg/day. It is made up mostly of Tamm-Horsfall mucoprotein, which is produced in the thick ascending loop of Henle. Low molecular weight proteins are found in the urine normally, but most are reabsorbed in the proximal tubule. Only small amounts of albumin are normally seen in the urine due to its charge and molecular weight, both factors inhibiting transport across the glomerular membrane. Excessive protein excretion occurs through 4 mechanisms:

- Disruption of the capillary wall barrier causing increased filtration of various plasma proteins—nephrotic syndrome
- Tubular damage that inhibits the normal resorptive capacity—Fanconi Syndrome
- Overflow with excess production of low molecular weight plasma proteins—light chains in multiple myeloma
- Increased secretion of tissue proteins associated with inflammation—pyelonephritis

There are 3 commonly used ways to assess proteinuria: the dipstick, 24-hour urine collection, and the protein creatinine ratio (P/Cr). The dipstick is useful only if positive, and then one should proceed with a more accurate measurement of the actual amount of protein excreted. It is susceptible to changes in the specific gravity of the urine, and as such, is not reliable.

The 24-hour collection is the gold standard, but unreasonable for an insurance population. The P/Cr is more convenient and highly correlated to the 24-hour collection. As the test assumes an excretion of 1 gm of creatinine in 24 hours and men frequently excrete more and women less, Ginsberg in graphic form showed that the normal range for men is 17–250 mg/gm, and for women 25–355
mg/gm. First voided specimens may underestimate the amount of proteinuria given the known decrease in excretion seen in the recumbent position.\textsuperscript{8} False positive results can be seen in highly alkaline urine and with hemoglobin and vaginal secretions. Nevertheless, it is still considered the most efficient method of measurement for the insurance population.

Proteinuria can present in various forms:

- Transient
- Functional
- Orthostatic
- Disease related, which can be nephrotic or non-nephrotic

Functional proteinuria is seen in dehydration, emotional stress, fever, heat injury, inflammatory processes, intense activity, and acute illnesses, mostly because of increased cardiac output seen in these states.

Orthostatic proteinuria is defined as significant proteinuria that appears during the day but is not present in a first voided specimen. It is seen in 3\%–5\% of the healthy young adult population. It usually is seen in individuals <35 years old, with excretion of less than 1 gm but occasionally up to 3 gm, and always with normal urine sediment. It is a benign condition.\textsuperscript{9}

In disease-related proteinuria the degree of proteinuria correlates with the progression of nephrotic syndrome or renal insufficiency.\textsuperscript{10,11} Mild proteinuria, if stable for “several years,” may not portend a more serious condition. However, if it exceeds 1 gm per 24 hours, there is a much greater likelihood that a significant glomerular lesion exists that can be defined by biopsy.

Nevertheless, random screening for proteinuria in the general population is not cost effective, unless it is selectively directed to high-risk groups such as the elderly and those with hypertension.\textsuperscript{12}

Microalbuminuria

Of the US population over age 6, 7.8\% have microalbuminuria (MA) with a progressive increase in prevalence with advancing age.\textsuperscript{13} The overall prevalence of MA in black males is 7.7\%, 5.4\% in Mexican-Americans, and 5.7\% in non-hispanic, white males. In the population over 20 years of age without clinical proteinuria, the incidence of MA is 29\% in those with diabetes mellitus, 16.8\% in hypertensives, 15.9\% in those with evidence of cardiovascular disease, and 3.3\% in healthy adults.

Older age, minority race, diabetes, hypertension, abnormal serum creatinine, and left ventricular hypertrophy were all independently associated with the presence of albuminuria after adjusting for other variables. Depending on the methodology (units) used by the lab, microalbuminuria is defined as 3–30 mg/dL, 30–300 mg/24-hour, 30–300 mg/gm creatinine, 30–300 mcg/mg creatinine, or 0.03–0.3 gm/gm creatinine.

Microalbuminuria is associated with disturbances in glucose metabolism,\textsuperscript{14} insulin resistance,\textsuperscript{15} and a more adverse pattern of cardiovascular risk factors.\textsuperscript{16} There are several theories as to the mechanism of vascular disease associated with MA. Pedrinelle and colleagues\textsuperscript{17} have proposed that the glomerular albumin leak reflects widespread atherosclerosis-mediated damage to the capillary network. Festa et al\textsuperscript{18} have shown an association of the level of C-reactive protein and fibrinogen with the presence of MA in both type 2 diabetic and nondiabetic individuals. They feel this is evidence of chronic inflammation as a potential mediator between MA and macrovascular disease. In a similar vein, Paisley et al\textsuperscript{19} provided evidence of an abnormality in nitric oxide (NO)-dependent macrovascular endothelial function remote from the kidney and of low-grade chronic inflammation that was associated with microvascular endothelial dysfunction in patients with proteinuria.

Albumin excretion correlates with the progression or renal insufficiency due to various etiologies.\textsuperscript{20} However, it is a modifiable risk factor.\textsuperscript{21,22} The use of angiotensin converting enzyme inhibitors and angiotensin-receptor antagonists such as Losartin have been
Table 1. Incidence (%) of Cardiovascular Events With and Without Microalbuminuria24

<table>
<thead>
<tr>
<th>Variables</th>
<th>With Microalbuminuria</th>
<th>Without Microalbuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI, stroke or CV death</td>
<td>25</td>
<td>13.9</td>
</tr>
<tr>
<td>CHF</td>
<td>8.5</td>
<td>2.5</td>
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<tr>
<td>No Diabetes History</td>
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<tr>
<td>MI, stroke or CV death</td>
<td>20.4</td>
<td>13.8</td>
</tr>
<tr>
<td>CHF</td>
<td>4.6</td>
<td>2.1</td>
</tr>
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shown to decrease the urinary albumin in type 2 diabetes mellitus patients independent of any associated reduction in blood pressure.23

The greatest area of concern is cardiovascular. Evaluation of data from the Heart Outcomes Prevention Evaluation (HOPE) Study by Gerstein et al24 showed a substantial difference in vascular endpoints based on the presence or absence of proteinuria (Table 1). MA appears to be a marker of generalized vascular disease and indicates an incremental risk for cardiovascular mortality in healthy individuals as well as those with known heart disease.25, 26

Patients with MA and hypertension have an increased incidence of insulin resistance, thicker carotid arteries, higher blood pressure (BP) levels, left ventricular hypertrophy, and higher cholesterol and triglyceride levels.27 Hypertensive patients with MA have a greater number of cardiovascular events than those without MA.28

It is well known that the presence of microalbuminuria in the adult onset diabetic and the nondiabetic is a marker for vascular disease. When underwriting such a case, it is essential not to look at albuminuria in isolation but to also determine the following factors:

- Amount of albuminuria
- Rate of progression
- Status of the urinary sediment
- Level of renal function

HEMATURIA

Hematuria is generally defined as greater than 3 to 5 red blood cells per high power field of freshly spun urine sediment. Ritchie et al29 reported that 2.5% of men undergoing routine screening were found to have microscopic hematuria. Others30 have even seen higher frequencies of hematuria, and as such routine screening without a specific indication is no longer recommended.31

Determining whether the blood is coming from the upper or lower parts of the urinary system is often difficult based on the urinalysis alone. If there are casts present, then one can generally be assured that the bleeding is from the kidney itself. Without casts some authors believe that the presence of dysmorphic red cells implies that the source is the upper tracts.32 One “rule of thumb” is that if 80% of the cells are dysmorphic, then the source is glomerular. If 80% are normal, then the source is the lower tract. Anything in between could be either.

The common causes of isolated hematuria33,34 are the following:

- Stones
- Cancer (75% of bladder cancers have painless hematuria)
- Analgesic nephropathy
- Sickle cell anemia
- IgA nephropathy35
- Benign recurrent hematuria (familial hematuria, thin glomerular basement membrane disease)
- Hypercalciuria (common in young children)

In children the most common causes are benign familial, renal malformations, infection, or hypercalciuria. Voiding cystourethrogram (VCUG) and ultrasound are the primary procedures assuming normal renal function and no proteinuria.

In adults the issues can be broken down
around the age of 50, because after that the risk of cancer steadily increases. The evaluation is different from children as malformations and genetic diseases, other than polycystic kidney disease (PCKD), are less likely to remain hidden until adulthood. The evaluation differs in that cystoscopy generally replaces VCUG. Studies have been done to devise an efficient method of evaluation of microscopic hematuria in the adult. Murakami et al studied 1217 asymptomatic adults with isolated microscopic hematuria with cystoscopy, intravenous pyelogram (IVP), and ultrasound. Of the group, 2.9% had highly significant lesions [24 cancers, 6 aggressive glomerulonephritis (GN)], and 18.9% had moderately significant lesions (108 less aggressive GN, 50 with urinary calculi among other findings). Of interest, the cystoscopy and ultrasound were 100% sensitive in diagnosing cancer, whereas the IVP missed 57.1% of the renal cancers. In those with a negative evaluation but persistent hematuria, they found no identifiable disease after 3 years of observation. Mairani et al did a similar study and their major additional contribution was the observation that the degree of hematuria was of diagnostic importance in separating out those with significant (glomerular) and life threatening (cancer) lesions.

Risk factors for significant underlying disease include: age older than 50, tobacco use, analgesic abuse, history of pelvic irradiation, cyclophosphamide, and exposure to occupational toxins such as dyes, benzenes, and aromatic amines.

With a negative evaluation, the prognosis is usually excellent in both adults and children. Empirical treatment with steroids or cytotoxic drugs is not indicated in view of the inherently benign prognosis. Within 5 years of discovery, 50% or more of such patients will have spontaneously remitted.

CASTS

Casts are cylindrical bodies made of Tamm-Horsfall protein that are several times larger than leucocytes and red blood cells. They are formed in the distal tubules and entrap cells there. Small numbers of hyaline and finely granular casts can be seen in normal urine. All other casts are abnormal. Granular casts often result from the degeneration of different cellular casts. The deeply pigmented or “muddy brown” type is the characteristic finding in acute tubular necrosis. Red blood cell casts are usually indicative of glomerulonephritis, but if the cells enter the urinary space via the tubular basement membrane, they can be seen in pyelonephritis also. In the latter condition, there will usually be white blood cell casts, bacteria and a positive urine culture. The presence of cellular casts can help in diagnosis but do not by themselves aid in prognosis. Factors such as renal function and the presence of hypertension are far more predictive of the severity of the disease.

CONTAMINANTS AND PROCESSING DELAY

A poorly obtained specimen may contain contaminants such as spores and pollens, fecal parasites, fibers, starch granules, and microbial overgrowth. Vaginal secretions and sperm may result in a positive dipstick for protein. A urinalysis done during menstruation may show up to 1.5 gm of protein that resolves with retesting in a week (personal medical observation). This is due to the plasma proteins present with red blood cells. Delayed processing may result in decreased clarity due to crystallization of solutes, rising pH, loss of ketone bodies, loss of bilirubin, and dissolution of cells and casts.

SUMMARY

The urinalysis is a source of significant information about the anatomy and function of the kidneys and urinary tract. It lends insights into the status of systemic diseases such as diabetes mellitus. Though not as exciting as many of the newly available diagnostic tests, it exceeds most for value per dollar spent.
REFERENCES

33. Yamagata K, Yamagata Y, Kobayashi M. A long-term follow-up study of asymptomatic hematuria


