Renal Function Tests

Clinical Laboratory Procedures and Diagnosis

Edited by
Cristobal G. Duarte, M.D.

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Foreword

A variety of excellent publications have become available during recent years with respect to renal pathophysiology, renal physiology, and the clinical aspects of renal disease. However, most have not emphasized methods of evaluating renal function in health and disease. In my judgment, this book is an excellent treatise on laboratory nephrology.

Physicians who do renal function tests will find in this book technical information that enables them to develop diagnostic procedures that can be adapted to almost any clinical laboratory. This book will be helpful not only to the nephrologist but to all clinicians who consider it necessary to understand the complex interaction of the kidney with other organ systems. Furthermore, medical students will find this book an excellent guide to indications for laboratory procedures needed to evaluate kidney malfunctions as well as a guide to the interpretation of the results of laboratory assessment.

There have been significant advances during the last few years in the interpretation of the pathological processes that mediate renal disease, and now more patients than ever survive far-advanced impairment of kidney function through renal dialysis and transplantation. However, the commonly employed laboratory procedures for assessing renal function in the patient with renal disease have remained relatively unchanged.

Most physicians are now aware that a measurement of the blood urea nitrogen (BUN) tells little about the degree of impairment of renal function, particularly as contrasted with the serum creatinine. An abnormal serum creatinine is an important indicator of impaired renal function. When the creatinine value is abnormal, it may be advisable to undertake a more specific assessment of the renal disorder either through a determination of the creatinine clearance or through the use of even more quantitative assessments, including standard clearance studies. The modern adaptation of radiolabeled compounds as a means of measuring glomerular and tubular function is well outlined in this excellent book.

The single most valuable test of renal function is the complete analysis of the urine and the microscopic examination of the urine sediment. The patient who has an abnormal urinalysis or an elevation in serum creatinine deserves a more complete assessment through quantitation of glomerular or tubular function, or both. This is especially important because renal function may be seriously impaired even when one or both of these two procedures yield normal results.

It is imperative that the student of medicine appreciate the fact that the intravenous urogram measures only renal mass (size) and serves little purpose in the quantitative assessment of renal function. However, functional capacity of the individual kidneys should probably be evaluated in any patient who has abnormal urinalysis, serum creatinine, or intravenous urogram.

No laboratory assessment of renal function, individually or in combination, should replace a careful study of the patient by a complete medical history and physical examination. The extent of diagnostic evaluation needed for the patient with hypertension, seriously impaired renal function, or genitourinary symptoms should be determined in accordance with the findings of the history and physical examination. Furthermore, renal histopathology, renal angiography, renal venous renin activity measurements, and studies of aldosterone metabolism can be interpreted with accuracy only in light of all clinical information.

This book stimulates a greater awareness of the need for and value of an accurate assessment of renal function by methods that are more informative than those employed by most physicians. I congratulate the editor and the authors of the individual chapters on their contributions to clinical nephrology.

James C. Hunt

Preface

It was with hesitation but with a deep sense of humility that I accepted the task of organizing the writing of this book on diagnostic nephrology, now being added to the excellent Series in Laboratory Medicine published through the years by Little, Brown and Company.

I believe that I was selected as editor of this book at least in part because at the time I was director of the Laboratory of Renal Function at Mayo Clinic. Therefore, due credit is given to those who have been instrumental in creating this laboratory and in maintaining its high standards of excellence: Doctors Frank T. Maher, James C. Hunt, Cameron G. Strong and David M. Wilson.

Included in the first two chapters are some results of original studies on renal function. This research could not have been completed without the able assistance of Mr. Robert R. Liedtke, Supervisor of Laboratory Nephrology.

C. G. D.

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Notice

The indications and dosages of all drugs in this book have been recommended in the medical literature and conform to the practices of the general medical community. The medications described do not necessarily have specific approval by the Food and Drug Administration for use in the diseases and dosages for which they are recommended. The package insert for each drug should be consulted for use and dosage as approved by the FDA. Because standards for usage change, it is advisable to keep abreast of revised recommendations, particularly those concerning new drugs.

Contents

1. Creatinine

Cristobal G. Duarte, Lila R. Elveback, and Robert R. Liedtke

A correct understanding of the concept of renal clearance is essential to the proper interpretation and evaluation of the results of studies of renal function. Renal clearance has been defined as the volume of plasma, expressed in milliliters, cleared of a determined substance in its passage through the kidneys in a unit time, usually 1 minute. The function of the kidneys in general, and of its physiological unit, the nephron, in particular, can be divided into the two main processes of glomerular filtration and tubular transport. This chapter and the first part of the next chapter will be concerned with concepts related to the glomerular filtration rate (GFR).

Homer Smith [65] was the first to propose that in order to be accepted as valid for the measurement of GFR, a substance must fulfill the following requirements: it must be metabolically inert and nontoxic; it must have no intrinsic effect on renal function; and after being filtered freely at the glomerulus, it must be neither reabsorbed nor secreted by the renal tubules. In addition, its clearance rate must not be affected by any other substance; it must remain constant regardless of variations in plasma levels and urine flow; and it must be possible to measure its concentration in plasma and urine by simple, reliable, and precise laboratory methods.

The clearance of inulin, a polysaccharide of molecular weight of approximately 5000, fulfills all these requirements and thus is the standard method for the measurement of GFR. Inulin, however, is not in endogenous concentration in the body. Studies of renal clearance of inulin require the intravenous administration of a priming dose followed by a constant infusion in order to maintain the plasma concentration of inulin constant during the determination of GFR. This procedure must be performed by specialized technical personnel; it requires that urine and blood samples be collected at constant, well-timed intervals, that the bladder be empty at the beginning and end of each clearance period, and that the specimens collected be processed chemically to obtain values for the calculation of the clearance. Because of these difficulties, simpler alternative methods have been sought for the measurement of GFR (for a detailed discussion of inulin and the use of radioisotopes for the measurement of GFR, see Chapter 2; for technical information on measurement of the clearance of creatinine, see Chapter 3).

The finding that creatinine is concentrated in the urine more than most other endogenous substances eliminated by the kidneys [53] led to the use of creatinine as a test of renal function. Creatinine is an amino-acid product of protein

This work was done while Dr. Duarte was Director of Laboratory Nephrology, Mayo Clinic Foundation, Rochester, Minn.

metabolism that is derived from creatine [6, 8, 22]. The main sites of creatine synthesis are the liver, the pancreas, and the kidney [8], but the bulk of creatine is contained in muscle, where creatine is stored as creatine and phosphocreatine before it is further metabolized and released into the circulation as creatinine [33], which is then excreted in the urine. Creatinine, therefore, is in endogenous concentration in the body and does not need to be infused for studies of renal function.

Technical Considerations

Three methods have been used for the determination of creatinine in blood, plasma, serum, and urine. The first method, based on the Jaffe reaction [3, 4, 7], measures, in addition to true creatinine chromogens, noncreatinine chromogens that do not appear in the urine since they are not filtered at the glomerulus [26]. Noncreatinine chromogens are acetone, pyruvic and ascorbic acid, proteins, barbiturates, phenolsulfonphthalein, sodium sulfobromophthalein, and other unknown substances [20, 34]. Another method for the determination of creatinine is based on the Folin-Wu reaction [34] and measures only true creatinine chromogens. A significant improvement in the precision of the determination of creatinine over the two manual methods has been achieved by the adaptation of the Jaffe reaction to an automatic chemical analyzer (the Technicon AutoAnalyzer). True serum creatinine concentration [11] is overestimated by 21 percent for values lower than 1 mg/dl by the AutoAnalyzer method and by 90 percent by the method that measures total creatinine concentration (the Jaffe reaction). For values of true serum creatinine higher than 1 mg/dl [11], the readings are 10 percent higher with the AutoAnalyzer and 21 percent higher with the Jaffe reaction.

Of the three methods used to measure the clearance of creatinine [51], the AutoAnalyzer gives the best correlation with the clearance of inulin. The extra amount of noncreatinine chromogens measured in plasma by the AutoAnalyzer method neutralizes the creatinine appearing in the urine by tubular secretion according to the mathematical calculation used to determine the clearance of endogenous creatinine:

$$\text{Creatinine clearance (ml/min)} = \frac{\text{Urine creatinine (filtered + secreted) mg/dl} \times V \text{ ml/min}}{\text{Plasma creatinine (True creatinine chromogens + Noncreatinine chromogens) mg/dl}}$$

Simultaneous measurements of inulin clearance, the clearance of true creatinine, and the clearance of creatinine by the AutoAnalyzer [1] demonstrated that at normal levels of GFR, true creatinine clearance overestimated GFR by a mean of 46 percent and creatinine clearance by the AutoAnalyzer by a mean of 8 percent. As there is a moderate to significant reduction in renal function

[1], the clearance ratios of creatinine/inulin (measured by the AutoAnalyzer) increase and this can be explained by two factors: first, as the plasma concentration of creatinine rises, the tubular secretion of creatinine is enhanced; and second, at these levels of renal dysfunction the plasma concentration of true creatinine increases in greater proportion than plasma noncreatinine chromogens. At a GFR lower than 20 ml/min [44], as a maximal secretory rate of creatinine is reached, the clearance of creatinine decreases toward the clearance of inulin. Some studies reported that the clearance of creatinine was significantly higher than that of inulin in nephrotic patients than in nonnephrotic controls [4], but such results have not been corroborated by others [1].

It is generally recognized [1, 43, 45, 46] that the clearance of endogenous creatinine consistently exceeds simultaneous values of inulin clearance, thus indicating that there is a secretory mechanism for creatinine at all levels of renal function. The existence of an active secretory process for creatinine has been further substantiated by results demonstrating that endogenous creatinine/inulin clearance ratios decline toward unity during the administration of iodopyracet (Diodrast) and para-aminohippurate [14], phlorhizin [61], and caronamide [9], substances that block the secretion of creatinine. Occasional findings of endogenous creatinine/inulin ratios of less than one [17] in patients with peritonitis or congestive heart failure suggest that there may also be a reabsorptive process for creatinine.

Two main procedures are usually followed for the measurement of the clearance of creatinine: the urine may be collected for a period of 1 or 2 hours (short creatinine clearance) or over a period of 24 hours (long creatinine clearance). Blood samples are usually drawn at the beginning and end of the study for plasma creatinine determination. The long creatinine clearance has been considered to be a more physiological index of renal function [9] because factors that are known to influence the GFR (e.g., physical activity, the effects of drugs and medications, emotional tensions, dietary intake, and changes in intra-abdominal and venous pressure) are included in the clearance determination. A complete 24-hour urine collection, however, is extremely difficult to obtain. The following mistakes, which invalidate the test, have been noted in the course of a 24-hour urine collection [17, 69]: the first voiding, instead of being discarded, may be included in the collection; one or more specimens may be lost because of forgetfulness or because of the patient's micturating in the toilet in the course of defecation; the patient may turn over a sample of each voiding at the end of the study instead of pooling all the urine; the urine container may become full before the end of the study and subsequent voidings may be discarded; or the last specimen, instead of being added to the collection, may be discarded. The advantages of the short creatinine clearance are that the study can be performed under good technical control and that a complete urine collection can be successfully obtained over a short period of time.

It is important, therefore, to determine the degree of correlation between the short and the long creatinine clearance. In a study performed in 10 volunteers

(five male and five female laboratory personnel), we compared both clearances. Blood samples were drawn at hours 0, 1, and 24 under fasting conditions. The protocols that were followed for these studies are given in Chapter 3. The subjects were hydrated by the oral administration of water a half hour before the first blood sample was drawn at hour 0 and in the course of the first 1-hour collection. After the second blood sample was drawn at hour 1, the subjects resumed their usual activities, all the urine was collected for the following 23 hours, and another blood sample was drawn at hour 24. The results of the first 1-hour clearance and the total 24-hour clearance were compared; they are illustrated in Table 1–1. Because the results did not differ between the sexes, they were studied together statistically. The significantly higher urine flow and creatinine clearance and the lower plasma creatinine found in the short clearance studies were probably the result of the hydration. Others have demonstrated that the 1-hour and 24-hour creatinine clearances are similar [18, 54] but that this good correlation can be disrupted as a result of heavy hydration.

Normal Values and Factors Affecting Plasma Concentration and Clearance of Creatinine

The clearance of creatinine is increased and the plasma concentration of creatinine is reduced throughout pregnancy [63]. The clearance of creatinine determined in infants during the first week of life [16] was in the range of 12.8 to 57 ml/min/1.73 m^2 and increased progressively [70] to a mean of 113 ml/min/1.73 m^2 at age 3, when creatinine clearance acquired adult characteristics. Mean creatinine clearance in children 3 years old or younger [70] was 88 ml/min/1.73 m^2. During the third decade of life [41], creatinine clearance starts to decline from a mean of 110 ml/min/1.73 m^2 for men and 95 ml/min/1.73 m^2 for women to a mean of 37 ml/min/1.73 m^2 for males and 39 ml/min/1.73 m^2 for females in the ninth decade of life. Another study [56] reported that creatinine clearance remains constant until the fourth decade of life, when it starts to decline at a rate of 6.5 ml/min/1.73 m^2/decade. With the reduction of creatinine clearance with aging [29, 57] there also occurs a decrease in the urinary excretion of creatinine, which has been interpreted as being indicative of a reduction in muscle mass; however, the serum creatinine concentration remains constant. The higher values for creatinine clearance in men have been related to the larger muscle mass in this sex [18, 23, 24, 25].

Initially, values of creatinine clearance were expressed as a function of body weight [35], but since the basis for this correlation is the size of the muscular mass, such correction did not take into consideration the effects of obesity. At present, values for creatinine clearance are usually corrected for body surface area (1.73 m^2) using the empirical formula of Dubois [35] which, by taking into consideration height and weight, adjusts the results of creatinine clearance for obesity and crude total weight. When the results for creatinine clearance were corrected for lean body mass as determined by anthropometric measure-

Table 1–1. Comparison of 1-Hour and 24-Hour Creatinine Clearances

Subject	Sex and Age	Volume (ml/min)		Plasma Creatinine (mg/dl)		Creatinine Clearance (ml/min/1.73 m²)	
		1 hour	24 hours	1 hour *	24 hours *	1 hour	24 hours
1	F, 31	8.19	1.81	0.95	0.99	93	99
2	F, 34	11.25	1.64	1.01	1.04	106	97
3	F, 22	9.86	2.57	1.05	1.11	104	101
4	F, 57	10.23	1.96	1.00	1.08	95	88
5	F, 26	5.71	1.35	0.69	0.72	158	151
6	M, 47	4.34	1.65	1.33	1.38	81	81
7	M, 26	5.30	1.50	1.05	1.08	139	128
8	M, 34	1.03	2.78	0.90	0.93	122	121
9	M, 29	3.53	1.17	1.25	1.26	108	99
10	M, 34	10.18	2.92	1.05	1.08	105	106
Mean ± SE	—	6.96 ± 1.09	1.90 ± 0.21 †	1.03 ± 0.05	1.06 ± 0.05 †	111 ± 7.24	107 ± 6.56 ‡

* One-hour plasma creatinine: Mean of samples taken at hours 0 and 1; 24-hour plasma creatinine: mean of samples taken at hours 0 and 24. Significantly different from 1-hour collection: † $P < 0.001$; ‡ $P < 0.05$.

ments [18], it was possible to eliminate the statistical difference between the sexes. A better relationship was obtained by correlating creatinine to body content of potassium [35], either by the administration of an isotope of potassium or by natural potassium-40 activity, as measured in a whole-body counter. The usefulness of this expression, as applied to creatinine clearance, is based on the fact that two-thirds of total body potassium is in skeletal muscle, and since the content of potassium in body fat and bone is small, total body potassium is not affected by changes induced by obesity or fasting [35].

Normal values for plasma concentration of creatinine are in the range of 0.8 to 1.2 mg/dl in males and 0.6 to 0.9 mg/dl in females. Serial measurements taken throughout the day in adults [64] revealed that the clearance of creatinine decreases in the hours of deepest sleep (between 12:00 P.M. and 4:00 A.M.), but this variation was not observed in patients with congestive heart failure [3]. In samples taken at 4-hour intervals [64], a 5- to 17-percent variation in plasma concentration of creatinine was detected, and these fluctuations were not related to changes in creatinine clearance. Plasma concentration of creatinine was higher by 11 percent in the afternoon [18, 48, 49], and the urinary excretion of creatinine was elevated in the evening hours [49]. Fasting eliminated or minimized these variations [49] in plasma concentration and urinary excretion of creatinine. Determinations of creatinine clearance in the same subject over a period of years [68] demonstrated significant fluctuations in values, probably as a result of biological variations. Because of the significant fluctuations in plasma concentration of creatinine throughout the day, the time when a blood sample is drawn can have a significant influence on the results of the clearance [54]. It is recommended, therefore, that blood samples for plasma creatinine determinations be drawn in the morning under fasting conditions.

In studies conducted on normal kidney donors [48] it was found that after nephrectomy, hypertrophy and hyperplasia of the remaining kidney occur and that a functional response is already in evidence 24 hours after the operation. Seven days after the removal of the kidney [48], the function in the remaining organ was found to be 70 percent of the total preoperative creatinine clearance. Two to six years after the uninephrectomy, the clearance of creatinine in the remaining kidney varied from 71 percent [48] to 85 percent in females and 87 percent in males [15] of the values that were obtained before the operation. Measurements of several parameters of renal function in one study [15] indicated that the functional recovery in normal kidney donors was significantly better in males and that this sex difference was related to the stimulatory effect of testosterone on renal growth as well as the parenchymal damage resulting from urinary tract infections, which females are prone to develop.

The plasma concentration and urinary excretion of creatinine may be affected significantly by the content of creatine and creatinine in the food. The administration of a diet free from creatine and creatinine [5] causes a parallel decrease in the plasma concentration and urinary excretion of creatinine, although the clearance of endogenous creatinine does not change. Raw meat is high in creatine and has little creatinine [9], but the content of creatinine in-

creases progressively with the temperature as the meat is subjected to heat. Canned meat also has large amounts of creatinine [35], since creatine is converted to creatinine in the process of thermal sterilization. The consumption of a well-cooked steak (which is high in creatinine) causes a significant increase in the clearance of creatinine [9].

In view of the fact that it is in muscle where creatine is metabolized to creatinine [61], it is not surprising that the production of creatinine is related to muscle mass. Males have a larger muscle mass, and thus more creatinine is excreted in the urine of men than in that of women; infants have low urinary excretion rates of creatinine that increase with age [35]. Professional athletes, either males or females [35], have a higher rate of excretion of creatinine in the urine than do controls. In clinical myopathies, in which the muscular mass is diminished [10, 55], the urinary excretion of creatine increases because the muscles are unable to metabolize fully the creatine released from the liver, pancreas, kidneys, and other organs, and since the endogenous production of creatinine is diminished [66], the urinary excretion and plasma concentration of creatinine are low [32], the plasma concentration of creatinine does not increase appropriately in relation to the impairment in renal function [32], and creatinine clearance must be calculated in order to obtain a better estimate of renal function [32]. In diseases such as tetanus, in which there is increased muscular activity [66], there may be an increase in the urinary excretion of creatinine. During heavy exercise, the urinary excretion of creatinine increases significantly [52, 67] and there is a decrease in creatinine clearance [52]. The urinary excretion of creatinine is increased in pyrexia [60].

The significantly low plasma concentration of creatinine and the high urinary excretion and clearance of creatinine in juvenile diabetics before the onset of renal disease [2] are probably related to the high levels of renal function in these patients resulting from high growth hormone activity [47]. Therefore, normal levels of plasma creatinine and creatinine clearance in diabetics [2] may be indicative of renal disease. With the onset of proteinuria [28], the values of creatinine clearance are lower in diabetics than in nondiabetic controls.

Creatinine and the Kidney: Theoretical Considerations

The validity of creatinine as a test of renal function is based on the assumption [42] that in a normal subject under steady-state conditions, as creatinine is released from muscle stores at a constant rate throughout the day, accumulation in the body is prevented by a renal excretory mechanism. Plasma concentration of creatinine, therefore [42], must be maintained at constant normal levels in a subject with a normal renal function, since the filtered load and urinary excretion of creatinine equal the amount of creatinine released from muscle. The dynamic changes in creatinine metabolism that have been postulated to take place as a result of variations in renal function [42] are demonstrated schematically in Figure 1–1. If creatinine is excreted exclusively by the kidneys by a process of glomerular filtration [42], a 50 percent reduction in renal function