**Calculation of the creatinine clearance**

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**OVERVIEW** — The creatinine clearance is a widely used test to estimate the glomerular filtration rate (GFR) [[1,2](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/1%2C2)]. Creatinine is derived from the metabolism of creatine in skeletal muscle and from dietary meat; it is released into the circulation at a relatively constant rate and has a stable plasma concentration. Like inulin, creatinine is freely filtered across the glomerulus and is neither reabsorbed nor metabolized by the kidney. However, tubular secretion by the organic cation secretory pathways in the proximal tubule accounts for approximately 10 to 20 percent of urinary creatinine in patients with a normal GFR and a progressively higher percentage as the GFR falls [[3](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/3)]. The net effect is progressive overestimation of the GFR with more severe disease. (See ['Increased creatinine secretion'](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance#H4) below.)

If the effect of secretion is ignored, then all of the filtered creatinine (equal to the product of the GFR and the serum creatinine concentration [SCr]) will be excreted (equal to product of the urine creatinine concentration [UCr] and the urine flow rate or volume [V]). Thus:

       GFR x SCr  =  UCr x V

       GFR = [UCr x V]/SCr

This formula is called the creatinine clearance and tends to exceed the true GFR by 10 to 20 percent or more depending upon the proportion of urinary creatinine that is derived from tubular secretion [[4](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/4)]. Historically, this error was balanced by an error of almost equal magnitude in the measurement of the serum creatinine. The error in serum creatinine measurement was due to non-creatinine chromogens (such as acetone, ascorbic acid, and pyruvate) that are present in serum and contributed 10 to 20 percent of the creatinine concentration measured by older colorimetric techniques. However, national standardization of serum creatinine assays to creatinine reference materials has largely abolished this error. If a laboratory is using standardized methods, creatinine clearance measurements will consistently be 10 to 20 percent higher than GFR in patients with a normal GFR and progressive higher as the GFR falls. (See ['Increased creatinine secretion'](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance#H4) below.)

The creatinine clearance is usually determined from a **24-hour** urine collection, since shorter collections tend to give less accurate results. One problem with shorter timed collections is that any retained urine would represent a larger percent of the total urine collection. In addition, creatinine excretion varies throughout the day [[5](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/5)]. (See ["Patient information: Collection of a 24-hour urine specimen (Beyond the Basics)"](http://www.uptodate.com/contents/collection-of-a-24-hour-urine-specimen-beyond-the-basics?source=see_link).)

**Example** — Suppose that the following 24-hour urine results are obtained in a 60 kg woman:

 SCr    =   1.2 mg/dL (106 micromol/L)
 UCr    =   100 mg/dL (8800 micromol/L)
 V       =   1.2 L/day

Thus:

 CCr   =  [100 mg/dL x 1.2 L/day] / 1.2 mg/dL = 100 L/day

To convert this value into units of mL/min, it has to be multiplied by 1000 to convert into mL and then divided by 1440 (the number of minutes in a day):

 CCr   =  [100 L/day x 1000 ml/L] /1440 min/day = 70 mL/min

A creatinine clearance calculator is provided ([calculator 1](http://www.uptodate.com/contents/calculator-creatinine-clearance-measured?source=see_link)), and the results should ideally be normalized to a body surface area (BSA) of 1.73 m2; BSA can be computed using a different calculator ([calculator 2](http://www.uptodate.com/contents/calculator-body-surface-area-mosteller-square-root-method?source=see_link)).

As an example, a creatinine clearance of 70 mL/min in a small woman with a weight and height of 50 kg and 160 cm, who has a BSA of 1.5 kg/m2, is normalized to a BSA of 1.73 m2 as follows:

CCr x 1.73/BSA = [70 mL/min x 1.73] / 1.5 = 80 mL/min per 1.73 m2

For a large person with a body surface area of 1.9 kg/m2, the adjusted CCr would be 64 mL/min per 1.73 m2.

The normal value for the creatinine clearance is 95 ± 20 mL/min per 1.73 m2 in women and 120 ± 25 mL/min per 1.73 m2 in men [[2](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/2)]. Thus, a level of 70 mL/min in a woman suggests the loss of approximately 25 percent of her GFR.

**LIMITATIONS** — There are three major errors that can limit the accuracy of the creatinine clearance as an estimate of GFR: errors in urine collection; increases in both creatinine secretion and extrarenal creatinine degradation as the GFR falls [[1,6](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/1%2C6)]. Because of these limitations and because a stable serum creatinine concentration usually reflects stable kidney function, many clinicians estimate the GFR from the serum creatinine concentration using derived estimation equations rather than a timed urine collection. The estimation equations are described in detail elsewhere. (See ["Assessment of kidney function", section on 'Estimation equations'](http://www.uptodate.com/contents/assessment-of-kidney-function?source=see_link&anchor=H20659769#H20659769).)

**Errors in urine collection** — An incomplete urine collection will lead to an underestimate of creatinine excretion and therefore of the GFR, while an overcollection (more than 24 hours) will lead to an overestimate of creatinine excretion and therefore of the GFR. (See ["Patient information: Collection of a 24-hour urine specimen (Beyond the Basics)"](http://www.uptodate.com/contents/collection-of-a-24-hour-urine-specimen-beyond-the-basics?source=see_link).)

The completeness of the collection can be estimated from knowledge of the normal rate of creatinine excretion, which is equal to creatinine production in the steady state. In adults under the age of 50, daily creatinine excretion should be 20 to 25 mg/kg (177 to 221 micromol/kg) lean body weight in men and 15 to 20 mg/kg (133 to 177 micromol/kg) lean body weight in women [[7](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/7)]. From the ages of 50 to 90, there is a progressive 50 percent decline in creatinine excretion (to about 10 mg/kg in men), due primarily to a fall in muscle mass. The above patient, for example, excreted 1200 mg (10,600 micromol) of creatinine or 20 mg/kg (177 micromol/kg), suggesting that the collection is probably complete.

**Example** — The creatinine clearance is calculated on two separate occasions in a patient with known renal disease and a stable weight and diet. Despite identical serum creatinine concentrations, the results from the second collection suggest that the creatinine clearance has declined by 20 mL/min. However, this interpretation contrasts with the stability of the patient’s weight (muscle mass), diet, and serum creatinine. Based upon the formula for creatinine clearance derived above [UCr x V/SCr], the difference in creatinine clearance must be related to differences in creatinine excretion (UCr x V). There are two possible explanations: the reduced creatinine excretion in the second specimen reflects either an incomplete second collection or an overcollection in the first specimen.

**Increased creatinine secretion** — Even with an accurate urine collection, the accuracy of the creatinine clearance as a measurement of GFR is limited by the fact that, at a normal GFR, 10 to 20 percent of creatinine excretion is derived from secretion in the proximal tubule, resulting in the creatinine clearance being 10 to 20 percent higher than the GFR. As the GFR falls, the associated reductions in creatinine filtration and excretion will result in an increase in serum creatinine, which provides the signal for enhanced creatinine secretion. The increase in secretion counterbalances the reduction in creatinine filtration so that a steady state is reestablished in which creatinine excretion is maintained at the same level as creatinine production with a slightly higher creatinine concentration than before [[2,4,8-10](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/2%2C4%2C8-10)]. However, the increase in creatinine secretion will result in the creatinine clearance being a progressively greater overestimate of the GFR.

As an example, as the true GFR falls from 80 to 40 mL/min (as measured by the clearance of an accurate filtration marker such as inulin or radioisotopic iothalamate or DTPA) [[9,11](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/9%2C11)], the absolute amount of secreted creatinine can rise by more than 50 percent, accounting for as much as 35 percent of urinary creatinine [[2](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/2)]. In this setting, creatinine excretion is much greater than creatinine filtration. As a result, calculation of the creatinine clearance from a 24-hour urine collection will represent a large overestimate of the true GFR. The net effect is that the creatinine clearance may be normal (>90 mL/min) in about one-half of patients with a true GFR of 61 to 70 mL/min and one-quarter of those with a true GFR of 51 to 60 mL/min [[8](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/8)]. Some patients with advanced disease have a creatinine clearance that exceeds the GFR by more than twofold.

As a result, all that can be concluded is that the creatinine clearance determined from an accurately timed, preferably 24-hour urine collection represents an upper limit of what the true GFR may be. As an example, a creatinine clearance of 70 mL/min indicates decreased kidney function, although the GFR may be as low as 35 mL/min. Furthermore, the degree of creatinine secretion appears to vary with time, changing the creatinine clearance independent of alterations in the GFR [[9,10](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/9%2C10)]. In some cases, the change in creatinine clearance is discordant from that of the GFR (as measured by inulin or radioisotopic clearance). Thus, the creatinine clearance can fall modestly (suggesting disease progression) at a time when the GFR is actually increasing [[10,12](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/10%2C12)].

More accurate determination of the GFR requires measurement of an exogenous substance such as inulin, [iohexol](http://www.uptodate.com/contents/iohexol-drug-information?source=see_link), iothalamate, DTPA, or EDTA [[9,11](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/9%2C11)]. Inulin is the ideal filtration marker in that it is neither secreted nor reabsorbed, but inulin has not been approved for clinical use in the United States, and is expensive and difficult to handle. The other markers provide reasonable approximations of inulin clearance [[13](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/13)].

**Increased extrarenal creatinine degradation** — In patients with advanced renal failure (serum creatinine greater than 6 mg/dL [530 micromol/L), extrarenal creatinine degradation is increased due, at least in part to increases in intestinal bacterial overgrowth and bacterial creatininase activity [[14](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/14)]. As a result, the serum creatinine concentration is lower than would be expected from the GFR. This will falsely elevate the creatinine clearance, adding to the problem of increased creatinine secretion.

**Enhancing the creatinine clearance measurement** — Measurement of the more accurate inulin or iothalamate clearance is not routinely available. There are two alternatives that may provide a more accurate estimate of the GFR from a timed, preferably 24-hour urine collection in patients with a stable serum creatinine concentration: averaging the creatinine and urea clearances; and measurement of the creatinine clearance during the administration of [cimetidine](http://www.uptodate.com/contents/cimetidine-drug-information?source=see_link) A more commonly used approach in patients with a stable serum creatinine is to estimate the GFR from empirically derived estimation equations. The estimation equations are described in detail elsewhere. (See ["Assessment of kidney function", section on 'Estimation equations'](http://www.uptodate.com/contents/assessment-of-kidney-function?source=see_link&anchor=H20659769#H20659769).)

**Averaged creatinine and urea clearances** — An alternative in patients with moderate to advanced renal disease (serum creatinine >2.5 mg/dL [220 micromol/L]) is to take the average of the creatinine and urea clearances [[11,15,16](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/11%2C15%2C16)]:

                 CCr  +  CUrea

 GFR    =    ————————

                          2

The rationale for this formula is that clearance of creatinine overestimates the GFR due to creatinine secretion, whereas the clearance of urea underestimates the GFR since approximately 40 to 50 percent of the filtered urea is reabsorbed. Fortuitously, the two errors tend to be of similar magnitude in patients with moderate to advanced disease.

**Use of cimetidine** — [Cimetidine](http://www.uptodate.com/contents/cimetidine-drug-information?source=see_link), an organic cation like creatinine, can competitively diminish proximal tubule creatinine secretion [[4,17,18](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/4%2C17%2C18)]. In one study of 16 patients with underlying renal insufficiency, 400 mg of cimetidine was given as an oral priming dose followed by 200 mg every three hours; both the creatinine and inulin clearances were measured every three hours [[4](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/4)]. The ratio of the creatinine to inulin clearance at baseline was about 1.5 (range 1.14 to 2.27), indicating substantial creatinine secretion. The ratio fell to a mean of 1.02 in eight patients, but remained elevated (mean 1.33) in the remaining eight patients who had persistent urinary creatinine secretion. (See ["Drugs that elevate the serum creatinine concentration"](http://www.uptodate.com/contents/drugs-that-elevate-the-serum-creatinine-concentration?source=see_link).)

Higher doses of [cimetidine](http://www.uptodate.com/contents/cimetidine-drug-information?source=see_link) have been used in an effort to more reliably lower the creatinine clearance to the true GFR. These intensive cimetidine regimens include:

* A single 1200 mg oral dose with a urine collection obtained between the third and sixth hours and the serum creatinine concentration measured at the beginning and the end of the test [[4](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/4)].
* A loading dose of 1200 to 2000 mg (depending upon renal function) followed by 400 to 800 mg at regular intervals for 3 to 4 days [[17](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/17)]. On the test day, a 1.5 hour urine collection (three 30 min clearance periods) for creatinine clearance was performed, which was as accurate as the more cumbersome 24-hour collection.

The safety of high single doses of [cimetidine](http://www.uptodate.com/contents/cimetidine-drug-information?source=see_link) has not been established in a large number of patients; it has been suggested that a maximum single dose of 800 mg may be preferable in patients with renal insufficiency [[18](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/18)].

Techniques using [cimetidine](http://www.uptodate.com/contents/cimetidine-drug-information?source=see_link) to reduce creatinine secretion followed by urine collections of less than 24-hours require pretest water loading (up to 10 mL/kg) to assure a high urine flow rate and therefore accurate urine collections. Despite these various techniques designed to maximize blockade of creatinine secretion, there will remain intra- and inter-individual variability in the effect of cimetidine on blockade of creatinine secretion, which complicates the interpretation of a cimetidine creatinine clearance.

**Inability to detect mild kidney disease** — Nephron loss leads to compensatory hypertrophy and hyperfiltration in the normal or less affected nephrons. Because of this adaptive response, the GFR falls very little in mild kidney disease, and measurement of the creatinine clearance or use of an estimation equation will fail to detect the presence of disease. Mild kidney disease may be detectable by abnormal findings in the urinalysis, such as hematuria and/or proteinuria. (See ["Secondary factors and progression of chronic kidney disease", section on 'Intraglomerular hypertension and glomerular hypertrophy'](http://www.uptodate.com/contents/secondary-factors-and-progression-of-chronic-kidney-disease?source=see_link&anchor=H3#H3).)

Renal transplant donors who acutely lose half of their functioning nephrons represent a good example of this phenomenon. Despite the loss of nephrons, the GFR is approximately 70 percent of baseline at 10 to 14 days after donation and 75 to 85 percent of baseline at long-term follow-up. (See ["Evaluation of the living kidney donor and risk of donor nephrectomy", section on 'Long-term risk'](http://www.uptodate.com/contents/evaluation-of-the-living-kidney-donor-and-risk-of-donor-nephrectomy?source=see_link&anchor=H13#H13).)

In addition, in patients who begin with a normal GFR, mild to moderate percentage reductions in GFR produce only a small elevation in serum creatinine that may remain within the normal range and within the range of laboratory variability. As an example, a 10 to 15 percent fall in GFR will produce at most a 10 to 15 percent increase in serum creatinine. If, for example, the baseline serum creatinine is 0.8 mg/dL (71 micromol/L), the serum creatinine will only increase to 0.9 to 1.0 mg/dL (80 to 88 micromol/L).

These relationships have been demonstrated in a variety of disorders, including lupus nephritis and autosomal dominant polycystic kidney disease. In lupus nephritis, progressive glomerulosclerosis and nephron drop-out can occur during the healing phase with little reduction in GFR [[12,19](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/12%2C19)]. Similarly, in autosomal dominant polycystic kidney disease, the GFR remains stable for many years despite structural distortion due to expansion of kidney cysts [[20](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance/abstract/20)]. Thus, patients with kidney disease must also be monitored for other signs of disease progression, such as an increase in protein excretion or systemic blood pressure. (See ["Therapy of diffuse or focal proliferative lupus nephritis"](http://www.uptodate.com/contents/therapy-of-diffuse-or-focal-proliferative-lupus-nephritis?source=see_link) and ["Course and treatment of autosomal dominant polycystic kidney disease", section on 'Kidney size'](http://www.uptodate.com/contents/course-and-treatment-of-autosomal-dominant-polycystic-kidney-disease?source=see_link&anchor=H7#H7).)

**SUMMARY** — The creatinine clearance is a widely used test to estimate the glomerular filtration rate (GFR).

* Creatinine is derived from the metabolism of creatine in skeletal muscle and from dietary meat; it is released into the circulation at a relatively constant rate and has a stable serum concentration. Like inulin, creatinine is freely filtered across the glomerulus and is neither reabsorbed nor metabolized by the kidney. However, approximately 10 to 20 percent of urinary creatinine is derived from tubular secretion when the GFR is normal and progressively higher as the GFR falls and the serum creatinine rises. (See ['Overview'](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance#H1) above.)
* If a laboratory is using standardized methods for measuring the serum creatinine, then creatinine clearance measurements will be 10 to 20 percent higher than the GFR if the GFR is normal. The difference will be greater as the GFR falls and creatinine secretion increases. (See ['Overview'](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance#H1) above.)
* The creatinine clearance is usually determined from a 24-hour urine collection, since shorter collections tend to give less accurate results. (See ['Overview'](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance#H1) above.)
* The creatinine clearance is calculated by dividing the 24-hour urine creatinine by the serum creatinine; the 24-hour urine creatinine is equal to the urine creatinine concentration multiplied by urine volume ([calculator 1](http://www.uptodate.com/contents/calculator-creatinine-clearance-measured?source=see_link)). The creatinine clearance should ideally be normalized to body surface area of 1.73 m2 ([calculator 2](http://www.uptodate.com/contents/calculator-body-surface-area-mosteller-square-root-method?source=see_link)). (See ['Example'](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance#H16405048) above.)
* There are several limitations to measurement of the creatinine clearance. Thus, for many patients, ascertaining whether the GFR is changing or is stable can usually be determined by monitoring the serum creatinine concentration. (See ['Limitations'](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance#H2) above.)
* An incomplete urine collection leads to an underestimate of creatinine excretion and therefore of the GFR. The completeness of the collection can be estimated from knowledge of the normal rate of creatinine excretion. In adults under the age of 50, daily creatinine excretion should be 20 to 25 mg/kg (177 to 221 micromol/kg) lean body weight in men and 15 to 20 mg/kg (133 to 177 µmol/kg) lean body weight in women. After age 50, creatinine excretion falls progressively due to a decrease in muscle mass, and may be as low as 10 mg/kg. (See ['Errors in urine collection'](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance#H3) above.)
* The accuracy of the creatinine clearance is limited by the fact that as the GFR falls, the rise in the serum creatinine is partially ameliorated by enhanced creatinine secretion. As a result, all that can be concluded is that the creatinine clearance, assuming a complete 24-hour urine collection, represents an upper limit of the true GFR. (See ['Increased creatinine secretion'](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance#H4) above.)
* Two enhancements to the creatinine clearance measurement may provide a more accurate estimate of the GFR: measurement of the creatinine clearance during the administration of [cimetidine](http://www.uptodate.com/contents/cimetidine-drug-information?source=see_link); and averaging the creatinine and urea clearances in patients with a moderate to advanced decrease in kidney function. (See ['Enhancing the creatinine clearance measurement'](http://www.uptodate.com/contents/calculation-of-the-creatinine-clearance#H16405127) above.)

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