^{99m}Tc-Mercaptoacetyltriglycine Camera-Based Measurement of Renal Clearance: Should the Result Be Normalized for Body Surface Area?

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Testing the rate of creatinine clearance by measuring the level of creatinine in the blood and in a 24-h urine collection is a common method of evaluating renal function. The result is routinely normalized for body surface area (BSA). Alternatively, renal clearance can be measured by ^{99m}Tc-mercaptoacetyltriglycine (MAG3) renal imaging without the need for urine collection. Frequently, the ^{99m}Tc-MAG3 camera-based result is also normalized for BSA. **Methods:** I evaluated the need for BSA normalization of renal clearance measurements in ^{99m}Tc-MAG3 imaging studies from both a conceptual and a mathematic point of view. Both approaches involved analyzing the effect of patient size, that is, BSA, on the factors blood volume, renal blood flow, and amount of test substance present in the blood in the creatinine clearance method compared with the ^{99m}Tc-MAG3 camera-based method. **Results:** Both the conceptual and the mathematic analyses were consistent with a significant difference between the creatinine and ^{99m}Tc-MAG3 approaches to measuring renal clearance. Larger patients have larger kidneys, greater renal blood flow, higher renal clearances, larger blood volumes, more muscle mass, and higher BSAs than smaller patients. However, the concentration of creatinine in the blood of patients of any size with normal renal function is similar because the amount of creatinine released into the blood varies with patient muscle mass, which varies with blood volume. Because normalization for BSA is needed for creatinine clearance, a single reference range can be used for all patients. In the case of measurement of renal clearance with ^{99m}Tc-MAG3 imaging (assuming a constant dose), the concentration of tracer in the blood will vary inversely with patient size because blood volume varies with patient size. Thus, as patient size increases, the blood concentration of tracer will go down and compensate for the increase in renal blood flow and renal clearance, and conversely. Consequently, the ^{99m}Tc-MAG3 renal imaging study is self-correcting for BSA and no additional correction is needed. **Conclusion:** A conceptual and mathematic analysis suggests that, although normalization for BSA is necessary in the measurement of renal clearance by the standard creatinine clearance test, such normalization is inappropriate in the ^{99m}Tc-MAG3 camera-based imaging study because the ^{99m}Tc-MAG3 method is inherently self-normalizing for BSA.

Key Words: ^{99m}Tc-MAG3; kidneys; clearance; creatinine clearance; image analysis

J Nucl Med Technol 2013; 41:279–282
DOI: 10.2967/jnmt.113.128124

Renal clearance is commonly measured by either the creatinine clearance test, which requires a 24-h urine collection, or the ^{99m}Tc-mercaptoacetyltriglycine (MAG3) renal imaging study, which does not involve urine collection. The creatinine clearance method requires secondary normalization of the result for body surface area (BSA) because renal size and clearance vary with patient size (*1*).

However, the literature is inconsistent relative to the need to normalize the renal clearance result from ^{99m}Tc-MAG3 imaging studies. Although at least two publications concerning renal clearance measurement with imaging, one with ^{99m}Tc-MAG3 and one with ^{99m}Tc-diethyleltraminepentaacetic acid, did not use secondary normalization for BSA (*2,3*), most publications on this subject, all with ^{99m}Tc-MAG3, have applied secondary normalization for BSA (*4–9*).

I have performed a rigorous conceptual and mathematic analysis of the traditional method of determining creatinine clearance with 24-h urine collection and the method involving ^{99m}Tc-MAG3 camera-based imaging relative to the appropriateness of secondarily normalizing the results for BSA.

MATERIALS AND METHODS

Conceptual Analysis

For the conceptual analysis, I evaluated all pertinent factors and parameters that vary with change in patient size or that affect renal clearance of the test substance, either creatinine or ^{99m}Tc-MAG3. Specifically, I evaluated how change in size affects the various factors and parameters differently between the creatinine and ^{99m}Tc-MAG3 methods.

Mathematic Analysis

For the mathematic analysis, I first compared the traditional creatinine clearance equation with the standard ^{99m}Tc-MAG3 renal imaging equation. Then, I converted both equations into an innovative form that allows direct determination of the need to normalize any renal clearance equation for BSA.

Received Jun. 21, 2013; revision accepted Sep. 19, 2013.
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Published online Oct. 28, 2013.

RESULTS

Conceptual Analysis

In Tables 1 and 2, the column headers list several parameters that may vary with change in patient size, and the data show the expected changes for a small or large patient relative to an average-sized patient in the various parameters. For both the creatinine (Table 1) and the ^{99m}Tc-MAG3 (Table 2) renal clearance methods, renal size, renal blood flow, and blood volume will change in direct proportion to change in patient size or BSA. In addition, the extraction efficiency of glomerular filtration for creatinine or tubular secretion for ^{99m}Tc-MAG3 will not change with patient size.

However, the expected effect of change in patient size on the remaining parameters differs between the creatinine and ^{99m}Tc-MAG3 methods. Since blood creatinine originates mainly in muscle and muscle mass changes in proportion to patient size, the concentration of creatinine in the blood is relatively independent of patient size. In addition, renal clearance can be represented by blood flow multiplied by extraction efficiency and, since renal blood flow varies with patient size whereas extraction efficiency and blood creatinine concentration are relatively fixed, renal clearance of creatinine will vary with patient size. Thus, to use a reference range that is independent of patient size, the creatine clearance result must be normalized for BSA.

In contrast, the ^{99m}Tc-MAG3 renal clearance method does not involve measurement of the concentration of the test substance in blood but is based on the percentage of administered ^{99m}Tc-MAG3 that is taken up or localized in the kidneys by a certain time after injection. Because the amount of ^{99m}Tc-MAG3 that is injected affects the numerator and denominator of the renal clearance uptake ratio proportionally, the amount injected does not affect the result and can be thought of as the same amount for all patients. Consequently, the effective blood concentration of ^{99m}Tc-MAG3 will vary inversely with patient blood volume and patient size and, therefore, will compensate for the direct proportional variation in renal blood flow and clearance with patient size. Thus, the ^{99m}Tc-MAG3 renal imaging method for measuring renal clearance is inherently normalized and secondary normalization for BSA is inappropriate.

In general, on the basis of this conceptual analysis, if the amount of test substance that is cleared by the kidneys is compared with the amount in the blood on a per-milliliter basis, secondary normalization for BSA is required (e.g., creatine clearance method). However, if the amount of test substance that is cleared by the kidneys is compared with the amount in the blood on a per-total-blood-volume basis, that is, total amount administered, secondary normalization for BSA is inappropriate (e.g., ^{99m}Tc-MAG3 imaging method).

Mathematic Analysis

Fundamentally, renal clearance refers to the transfer of a test substance from blood or plasma into the kidney as a function of time. Two pieces of information are needed to calculate the clearance rate: the amount of substance transferred into the kidney during that period on a per-minute basis, U (mg/min), and the concentration of the substance in the blood or plasma that is available for clearance during the period over which the clearance is measured, B (mg/mL). In the case of the creatine clearance method, the relevant equation for renal clearance, Cl (mL/min), before normalization for BSA is

$$\mathrm{Cl\,(mL/min)} = \frac{\mathrm{U\,(mg/min)}}{\mathrm{B\,(mg/mL)}}. \qquad \text{Eq. 1}$$

TABLE 1
Parameters Affecting Creatinine 24-Hour Urine Renal Clearance

Patient size	Renal size	Renal blood flow	Blood volume	EE	Creatinine production	Creatinine bld conc	Creatinine excreted	BSA correction
Average	–	–	–	–	–	–	–	Yes
Small	↓	↓	↓	–	↓	–	↓	Yes
Large	↑	↑	↑	–	↑	–	↑	Yes

EE = extraction efficiency; bld conc = blood concentration; – = average or unchanged; ↓ = decreased; ↑ = increased.

TABLE 2
Parameters Affecting ^{99m}Tc-MAG3 Image-Based Renal Clearance

Patient size	Renal size	Renal blood flow	Blood volume	EE	Tracer dose	Tracer bld conc	Tracer uptake	BSA correction
Average	–	–	–	–	–	–	–	No
Small	↓	↓	↓	–	–	↑	–	No
Large	↑	↑	↑	–	–	↓	–	No

EE = extraction efficiency; bld conc = blood concentration; – = average or unchanged; ↓ = decreased; ↑ = increased.

The initial step of multiplying the concentration of creatinine in the 24-h urine collection by the urine volume has been omitted. When the creatinine clearance equation is normalized for BSA, the ratio 1.73 m^2/BSA_P is added, where 1.73 m^2 is the BSA of a normal-sized person and BSA_P is the BSA of the patient.

$$\text{Cl (mL/min)} = \frac{\text{U (mg/min)}}{\text{B (mg/mL)}} \times \frac{1.73\ m^2}{BSA_P}. \qquad \text{Eq. 2}$$

Equation 2 demonstrates that the renal clearance result with the creatinine clearance method is explicitly and secondarily normalized for BSA.

In the case of the ^{99m}Tc-MAG3 imaging method, the equation for renal clearance is

$$\text{Cl (mL/min)} = \frac{\text{A (mCi}_{kid}) \times \text{K (mL/min)}}{\text{D (mCi}_{inj})}. \qquad \text{Eq. 3}$$

Equation 3 measures renal clearance, Cl (mL/min), in terms of the amount of ^{99m}Tc-MAG3 activity cleared by the kidneys by a certain time after injection, A (mCi_{kid}), relative to the amount of ^{99m}Tc-MAG3 that was injected, D (mCi_{inj}). This percentage renal uptake is multiplied by a factor, K (mL/min), that converts the percentage renal uptake of ^{99m}Tc-MAG3 to renal clearance, Cl (mL/min). Correction for photon attenuation, which is unrelated to the present discussion, is ignored for the sake of simplicity and clarity. Now the question is whether the renal clearance result with ^{99m}Tc-MAG3 should be normalized for BSA.

First, it should be noted that in Equation 3 the amount of ^{99m}Tc-MAG3 injected, in the denominator, and the amount cleared by the kidneys, in the numerator, change proportionally with changes in the amount injected. Thus, once the equation is simplified for the amount injected, effectively every patient is injected with 1 mCi (37 MBq). Second, although the denominator of the creatine clearance equation is in terms of test substance per milliliter, the denominator of the ^{99m}Tc-MAG3 imaging method equation is effectively in terms of test substance per total blood volume, a significant difference.

If the total blood volume were known and it was used to convert the denominator into the form of test substance per milliliter, we would be adding a factor that varied with BSA and the renal clearance result would then have to be normalized for BSA just like the creatinine clearance method. Without the addition of the total blood volume factor in the denominator the equation is inherently normalized for BSA because the actual concentration of tracer in the blood will vary inversely with BSA since blood volume varies with BSA. And this effect is balanced by the increase in renal blood flow and clearance with BSA. No secondary normalization for BSA is needed.

Alternatively, the question of whether it is appropriate to secondarily normalize renal clearance results from ^{99m}Tc-MAG3 imaging studies for BSA can be evaluated with a mathematic approach that more directly incorporates the physiologic parameters in Table 1.

Starting with the creatinine clearance method, we convert the factor in the numerator that represents the amount of test substance cleared in a certain time to the factors that determine the amount of test substance that is cleared. These factors are blood flow to the kidneys, F (mL/min-kidneys), the extraction efficiency, EE (no units), for the test substance in question, which will depend primarily on the extraction mechanism, and the concentration of the test substance in blood as a function of time during the uptake period, $_0\int^t$ B dt (mCi-min/mL). Here, B is the concentration of creatinine or ^{99m}Tc-MAG3 in blood and t is the time from injection to the end of acquisition of the test substance in urine for creatinine or in the kidneys for ^{99m}Tc-MAG3. The final equation for creatinine uptake in the numerator is

$$\text{U(mg/kidneys)} = \text{F(mL/min-kidneys)} \times \text{EE} \times \int_0^t \text{B dt(mg-min/mL)}. \qquad \text{Eq. 4}$$

Substituting the right-hand side of Equation 4 into Equation 1 and expanding the factor B in both the numerator and the denominator gives

$$\text{Cl (mL/min)} = \frac{\text{F (mL/min-kidneys)} \times \text{EE} \times \int_0^t \text{TBCr (mg)/TBV (mL)dt (min)}}{\text{TBCr (mg)/TBV (mL)}}, \qquad \text{Eq. 5}$$

where TBCr is total blood creatinine and TBV is total blood volume. Now we can substitute either BSA or a 1 for each factor, depending on whether the factor is a physiologic entity that varies with patient size or not, respectively. This gives

$$\text{Cl (mL/min)} \sim \frac{\text{BSA} \times 1 \times \text{BSA/BSA} \times 1}{\text{BSA/BSA}}, \qquad \text{Eq. 6}$$

which reduces to

$$\text{Cl (mL/min)} \sim \text{BSA}, \qquad \text{Eq. 7}$$

indicating that renal clearance, as measured by the creatinine clearance method, varies with patient size and requires normalization for BSA.

If we repeat the process for the ^{99m}Tc-MAG3 imaging method starting with Equation 3 and ignore the conversion constant, we get

$$\text{Cl (mL/min)} = \frac{\text{F (mL/min - kidneys)} \times \text{EE} \times \int_0^t \text{D (mCi)/TBV (mL)dt (min)}}{\text{D (mCi)}}. \qquad \text{Eq. 8}$$

Substituting either BSA or 1 as above gives

$$\text{Cl (mL/min)} \sim \frac{\text{BSA} \times 1 \times \text{BSA/BSA} \times 1}{\text{BSA}}, \qquad \text{Eq. 9}$$

which reduces to

$$\mathrm{Cl\,(mL/min)} \sim 1, \qquad \text{Eq. 10}$$

indicating that renal clearance, as measured by the ^{99m}Tc-MAG3 imaging method, does not vary with patient size and is, therefore, inherently normalized for patient size. Secondary normalization for BSA is not appropriate.

DISCUSSION

Renal imaging with ^{99m}Tc-MAG3 is a widely used procedure that generates a variety of functional information about the kidneys and collecting systems as well as significant anatomic information. One particularly important functional parameter is renal clearance. When renal clearance is measured with the traditional creatinine clearance test, it is necessary to normalize the result for BSA. In the present paper I have shown that, when renal clearance is measured with the ^{99m}Tc-MAG3 imaging method, the result is inherently normalized for BSA and it is inappropriate to secondarily normalize the result for BSA.

Although there is uniform consensus in the literature that normalization for BSA is necessary in the creatinine clearance method of measuring renal clearance, the literature is inconsistent with respect to the use of secondary normalization for BSA in nuclear medicine imaging studies. There are two articles, one using ^{99m}Tc-MAG3 to evaluate renal clearance by tubular secretion and one using ^{99m}Tc-diethyleltraminepentaacetic acid to evaluate renal clearance by glomerular filtration, that appropriately did not use secondary normalization for BSA (*2,3*). On the other hand, there are several papers that evaluated renal clearance with ^{99m}Tc-MAG3 imaging that inappropriately normalized for BSA secondarily (*4–9*).

The analysis in this paper applies to the evaluation of renal clearance by any nuclear medicine imaging procedure no matter what radiopharmaceutical is used as long as the radiopharmaceutical is cleared by the kidneys. Renal clearance can also be evaluated by nonimaging nuclear medicine procedures. In general, these procedures are performed by injecting intravenously a radiopharmaceutical that is cleared by the kidneys, acquiring multiple blood samples over time, and measuring and analyzing the resulting time–activity curve. In the nonimaging approach, the result also does not need to be normalized for BSA because the parameters that determine the rate of clearance of the radiopharmaceutical from the blood, blood volume and kidney size, have opposite effects on clearance rate as they change with BSA and cancel.

Our conceptual and mathematic analysis shows that there is a fundamental difference between the creatinine clearance method and the ^{99m}Tc-MAG3 imaging method. In the creatinine clearance method the test substance is made by the patient's muscle and, therefore, the amount entering the blood will vary with patient size and blood volume. Thus, the concentration of creatinine in the blood will be relatively constant and will not vary with patient size. However, the measured creatinine renal clearance will vary with patient size because renal blood flow varies with patient size and, therefore, the amount of creatinine in the urine will vary with patient size. Normalization for BSA will be necessary.

On the other hand, in the ^{99m}Tc-MAG3 renal imaging method the amount of administered test substance is effectively the same for all patients and, therefore, the concentration of test substance in the blood will vary inversely with the patient's size and blood volume. This inverse relationship inherently normalizes for patient size and renal clearance, and secondary normalization for BSA is inappropriate.

In general, renal clearance in ^{99m}Tc-MAG3 imaging studies is calculated using software provided by the γ-camera vendor. Usually, the software was written some time ago and documentation for the software is limited. Unfortunately, the vendor frequently cannot provide the exact algorithm and cannot confirm whether the algorithm secondarily normalizes for BSA (*2*). If the vendor software for calculation of renal clearance with ^{99m}Tc-MAG3 includes a secondary normalization for BSA, the results will be incorrect.

CONCLUSION

The ^{99m}Tc-MAG3 renal imaging study is a widely used method for evaluating renal function and, in particular, for quantitating renal clearance. Although normalization for patient size is necessary in the traditional creatinine clearance method of measuring renal clearance, I have demonstrated that normalization is inherent in the ^{99m}Tc-MAG3 renal imaging method and that secondary normalization for patient size is inappropriate.

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