Creatinine Clearance as a Substitute for the Glomerular Filtration Rate in the Assessment of Glomerular Hemodynamics

Noriyuki Okada, Masahito Imanishi, Katsunobu Yoshioka, Yoshio Konishi, Michiaki Okumura, Shiro Tanaka, and Satoru Fujii

A method for the clinical assessment of glomerular hemodynamics has been published previously. We here examined whether, when using this method, renal creatinine clearance (Ccr) can be substituted for the glomerular filtration rate (GFR). The study subjects comprised 57 inpatients from Osaka City General Hospital: 30 with type 2 diabetes mellitus and 27 with chronic glomerulonephritis. During the 2-wk study, patients received a high-salt diet for 1 wk and a low-salt diet for 1 wk. Urinary sodium excretion and systemic blood pressure were measured daily. The renal plasma flow, Ccr, and plasma total protein concentration were also evaluated simultaneously on the last day of the high-salt diet. The GFR was also calculated from the fractional renal accumulation of 99mTc-diethylenetriaminepentaacetic acid (DTPA). Glomerular hemodynamics, represented by the glomerular capillary hydraulic pressure and the resistance of afferent and efferent arterioles, were calculated using the renal clearance, the plasma total protein concentration, and the pressure-natriuresis relationship. Values for renal hemodynamics with the Ccr-derived GFR were compared with those from the 99mTc-DTPA-derived GFR. Ccr values of 53 to 169 ml/min correlated with the 99mTc-DTPA-derived clearance of 39 to 179 ml/min (n = 57, r = .71, p < .001). Values for the glomerular pressure and the resistances of afferent and efferent arterioles calculated using the Ccr-derived GFR correlated significantly with those calculated using the 99mTc-DTPA-derived GFR (r = .99, p < .001 and r = .99, p < .001, respectively). These results indicate that the Ccr is an accurate representation of the GFR for use in glomerular hemodynamic analysis of the pressure-natriuresis relationship. (Hypertens Res 1999; 22: 279-284)

Key Words: renal hemodynamics, creatinine clearance, pressure-natriuresis curve, diabetic nephropathy, chronic glomerulonephritis

Based on the results of numerous experimental studies, abnormalities of glomerular hemodynamics, e.g., glomerular hypertension, are thought to play a key role in the progression of chronic renal disease (1-5). Despite the evident importance of glomerular hemodynamics, however, a method for their direct clinical assessment in humans has only recently been proposed (6-8). In this method, glomerular hemodynamics, i.e., glomerular capillary hydraulic pressure and afferent and efferent glomerular arteriolar resistance, are calculated from renal clearance, total plasma protein concentration, and the pressure-natriuresis relationship. Renal clearance refers to the glomerular filtration rate (GFR) and the renal plasma flow (RPF). An exact GFR is obtained by measuring the renal clearance of inulin, 125I-iothalamate, or 99mTc-diethylenetriaminepentaacetic acid (DTPA). However, because the repeated use of these agents is impractical for both economic and safety reasons, creatinine clearance (Ccr) usually is used to estimate the GFR.

In this study, we investigated whether the Ccr can be used to substitute for the GFR in the clinical assessment of glomerular hemodynamics.

Methods

Patients
We evaluated 30 inpatients with type 2 diabetes (NIDDM) (16 men and 14 women; mean ± SD, 61 ± 10 yr; range, 19-70 yr) and 27 inpatients with chronic glomerulonephritis (CGN) (11 men and 16 women; mean ± SD, 46 ± 15 yr; range, 20-68 yr) at Osaka City General Hospital. Type 2 diabetes was diagnosed by the criteria of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (9). CGN was established histologically by renal biopsy more than 1 wk before the study. Twenty five of the 27 patients had IgA nephropathy and 2 of the 27 had focal glomerular sclerosis. Informed consent was obtained from all patients and the study was approved by the Institutional Ethics
Committee in accordance with the Code of Ethics of the World Medical Association (10, 11). Table 1 shows the characteristics of the patients at the start of the study. Differences in the mean values between the two groups were not statistically significant except for age, which was significantly higher in patients with type 2 diabetes (p < .0001).

Study Protocol
This study was performed after plasma glucose levels and blood pressure had been brought under control by diet or medication over at least 2 wk of hospitalization. In order to examine the pressure-natriuresis relationship, patients received both a 1-wk low-salt diet (approximately 5 g of salt daily) and a 1-wk high-salt diet (approximately 15 g of salt daily), given consecutively and in random order. The total daily calories and total protein were kept constant. On each of the last 3 d of each diet, 24-h urine collections were performed and the urine was assayed for sodium and creatinine. Urinary excretion of sodium was assessed as the mean values obtained on the last 3 d of each diet. The SD of the 3 values of urinary sodium excretion rate (UNaV) ranged from 5% to 35% of the mean value of UNaV in each patient. On the last day of each diet, a 24-h record of hourly blood pressure was obtained by a portable monitor using an oscillometric technique (Listmini, BP-8800, Colin Co., Aichi, Japan). The mean arterial pressure (MAP) was calculated by adding one third of the pulse pressure to the diastolic pressure, using the mean values from the 24-h record. RPF, GFR, and Ccr were measured simultaneously while the patient was supine. The reliability of the values for Ccr was confirmed by measurement of serial 24-h creatinine clearances on the last 3 d of the high-salt diet. The SD of the 3 values of Ccr ranged from 3% to 30% of the mean value of Ccr in each patient. The results for RPF, GFR, and Ccr were reproducible, and were standardized for a body surface area of 1.73 m².

Calculation of the Pressure-Natriuresis Curves and Glomerular Hemodynamics
Pressure-natriuresis curves (6, 13) were constructed by plotting the UNaV as a function of the MAP. Assuming a linear relation between MAP and UNaV, a pressure-natriuresis curve for each patient during each sodium diet may be drawn by linking the two points obtained when the patient's sodium balance is in a steady state. We expressed the MAP as the mean of the 24 values in the 24-h record, and calculated the mean UNaV for the last 3 d of each diet. The extrapolated intercept, A (mmHg), on the x-axis of the pressure-natriuresis curve and the slope, B (mmol/d per mmHg), were calculated as follows (6, 7):

\[
A = \frac{UNaV(H) \times MAP(L) - UNaV(L) \times MAP(H)}{UNaV(H) - UNaV(L)} \quad (1)
\]

\[
B = \frac{UNaV(H) - UNaV(L)}{MAP(H) - MAP(L)} \quad (2)
\]

where (H) and (L) denote the steady state results during high- and low-salt diets, respectively. With A and B, UNaV can be expressed as a function of MAP (6, 7):

\[
UNaV = B \times (MAP - A) \quad (3)
\]

We assumed that “A” of the pressure-natriuresis relationship denotes the critical blood pressure be-

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the Patients at the Start of the Study</th>
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<tr>
<td>Sex (male/female)</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>(19, 70)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
</tr>
<tr>
<td>(19.6, 29.9)</td>
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<tr>
<td>Serum creatinine (mg/dl)</td>
</tr>
<tr>
<td>(0.4, 1.1)</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
</tr>
<tr>
<td>(103, 154)</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
</tr>
<tr>
<td>(65, 96)</td>
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<tr>
<td>Mean arterial pressure (mmHg)</td>
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<td>(83, 117)</td>
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</table>

Values are expressed as the mean±SD. The ranges of ages, serum creatinines, systemic blood pressures and diastolic blood pressures are shown in parentheses. NIDDM, non-insulin-dependent diabetes mellitus; CGN, chronic glomerulonephritis.
low which glomerular filtration ceases, predicted by eq. 3 and corresponding to the sum of the pressure drop from the heart to the glomeruli plus the pressures opposing filtration at the glomeruli. Thus, the effective filtration pressure, $\Delta P_F$, across the glomerular capillary walls can be estimated as the difference between the MAP and $A$ ($6, 7, 14$):

$$\Delta P_F = MAP - A$$

(4)

Because $\Delta P_F$ is the difference between the glomerular capillary pressure ($P_{GC}$) and the sum of the pressure against filtration, $P_{GC}$ can be represented as:

$$P_{GC} = \Delta P_F + P_T + \Pi_G$$

(5)

where $P_T$ is the hydraulic pressure in Bowman’s space, assumed to be 10 mmHg, and $\Pi_G$ is the mean oncotic pressure within the glomerular capillaries, estimated from the mass balance law of plasma protein during glomerular ultrafiltration ($6, 7, 15$).

$\Pi_G$ can be obtained from the formula as ($6, 7$):

$$\Pi_G = 5 \times (C_M - 2)$$

(6)

where $C_M$ is the mean concentration of protein in the plasma of glomerular capillaries. $C_M$ is calculated on the basis of the mass concentration law of plasma protein during glomerular ultrafiltration as follows:

$$C_M = \frac{TP \times \ln \left( \frac{1}{1 - FF} \right)}{FF}$$

(7)

where FF is the filtration fraction (=GFR/RPF).

Glomerular hemodynamics are described in four ways: the $P_{GC}$, the whole-kidney ultrafiltration coefficient ($K_f$), the resistance of afferent arterioles ($R_A$), and the resistance of efferent arterioles ($R_E$) ($6, 7$). On the basis of Ohm’s law, $R_A$ is calculated as the value “MAP - $P_{GC}$” divided by the renal blood flow. $R_E$ is calculated as the difference between the total renal vascular resistance and $R_A$.

$P_{GC}$ in our study is an estimation based on the pressure-natriuresis relationship, since it cannot be measured directly in humans. Where the MAP intercepts the x-axis of the pressure-natriuresis curve, the urinary excretion of sodium approaches zero because of the decrease of both the GFR and the effective filtration pressure (see eq. 4, above) ($6, 7, 16$). The difference between the MAP and the x-intercept, extrapolated from the pressure-natriuresis relationship, can be assumed to be the $\Delta P_F$, the effective filtration pressure across the glomerular capillary walls ($6, 7$). The $\Delta P_F$ plus the oncotic pressure within the capillaries equals the transcapillary difference in pressure, which equals $P_{GC}$ minus the hydrostatic pressure in Bowman’s space, a small and nearly constant pressure of approximately 10 mmHg. Thus $P_{GC}$ equals the sum of $\Delta P_F$, the hydrostatic pressure in Bowman’s space, and the oncotic pressure within the glomerular capillaries (see eq. 5, above). It is necessary to know the GFR to obtain the oncotic pressure within the glomerular capillaries (see eq. 6 and 7, above).

**Statistical Analysis**

The values used for statistical analysis of glomerular hemodynamics and mean arterial pressure were those measured during the diet with a high salt level. Results were expressed as mean ± SD except for the resistance of glomerular arterioles and the whole-kidney ultrafiltration coefficient, which were expressed as mean and range because the values for the patients were not normally distributed. The significance of differences of age, serum creatinine and systolic blood pressure between the patients with diabetes and those with chronic glomerulonephritis was evaluated by Student’s t test for nonpaired samples. The significance of differences between Ccr and the clearance of $^{99m}$Tc-DTPA was examined by Student’s t test for paired samples. The correlation coefficient for the Ccr vs. the GFR by $^{99m}$Tc-DTPA, and between the two $P_{GC}$s calculated from the Ccr and the accumulation of $^{99m}$Tc-DTPA were evaluated by the least-squares method. This method was also used for $R_A$, $R_E$ and $K_f$. Stat View J. software (ver. 4.5; Abacus Concepts, Inc., Berkeley, CA) was used for all analyses. P values less than .001 were considered statistically significant.

**Results**

The relationship between the urinary excretion of sodium and the mean arterial pressure (pressure-natriuresis curve) is shown in Fig. 1. Table 2 compares renal hemodynamics in Ccr-derived and $^{99m}$Tc-DTPA-derived GFRs in patients receiving high-salt diets. The Ccr-derived GFR was 19% higher than the $^{99m}$Tc-DTPA-derived GFR; the
The correlation of Ccr with $^{99m}$Tc-DTPA in the calculation of the GFR was significant ($N=57$, $r = .71$, $p < .001$, Fig. 2). Values of $P_{GC}$, $R_A$ and $R_E$ calculated with Ccr-derived GFRs correlated significantly with those calculated with the $^{99m}$Tc-DTPA-derived GFRs ($r = .99$, $p < .001$, Fig. 3; $r = .99$, $p < .001$, Fig. 4A; and $r = .99$, $p < .001$, Fig. 4B, respectively, $N=57$). $K_f$ calculated with the Ccr-derived GFR correlated significantly with that calculated with the $^{99m}$Tc-DTPA-derived GFR ($N=57$, $r = .99$, $p < .001$).

The correlation of Ccr with $^{99m}$Tc-DTPA in the calculation of the GFR was not significant ($N=30$, $r = .46$, $p = .009$). Values of $P_{GC}$, $R_A$ and $R_E$ calculated with Ccr-derived GFRs correlated significantly with those calculated with the $^{99m}$Tc-DTPA-derived GFRs ($r = .99$, $p < .001$; $r = .99$, $p < .001$; and $r = .99$, $p < .001$, respectively, $N=30$). $K_f$ calculated with the Ccr-derived GFR correlated significantly with that calculated with the $^{99m}$Tc-DTPA-derived GFR ($N=30$, $r = .99$, $p < .001$).

In the patients with CGN, the correlation of Ccr with $^{99m}$Tc-DTPA in the calculation of the GFR was not significant ($N=27$, $r = .83$, $p < .001$). Values of $P_{GC}$, $R_A$ and $R_E$ calculated with Ccr-derived GFRs correlated significantly with those calculated with the $^{99m}$Tc-DTPA-derived GFRs ($r = .99$, $p < .001$; $r = .99$, $p < .001$; and $r = .99$, $p < .001$, respectively, $N=27$). $K_f$ calculated with the Ccr-derived GFR correlated significantly with that calculated with the $^{99m}$Tc-DTPA-derived GFR ($N=27$, $r = .99$, $p < .001$).

Table 2. Renal Hemodynamics on a High-Salt Diet as Calculated Using Ccr-Derived and $^{99m}$Tc-DTPA-Derived GFRs ($N=57$)

<table>
<thead>
<tr>
<th></th>
<th>Ccr-derived GFR</th>
<th>$^{99m}$Tc-DTPA-derived GFR</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance (ml/min)</td>
<td>107±22</td>
<td>94±29</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>$P_{GC}$ (mmHg)</td>
<td>47±9</td>
<td>46±8</td>
<td>.003</td>
</tr>
<tr>
<td>$R_A$ (dynes-cm$^{-5}$)</td>
<td>6,100</td>
<td>6,300</td>
<td>.007</td>
</tr>
<tr>
<td>(2,100, 16,800)</td>
<td>(2,100, 16,900)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$R_E$ (dynes-cm$^{-5}$)</td>
<td>5,800</td>
<td>5,700</td>
<td>.001</td>
</tr>
<tr>
<td>(1,800, 16,100)</td>
<td>(1,800, 16,000)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$K_f$ (ml/s per mmHg)</td>
<td>0.351</td>
<td>0.328</td>
<td>.038</td>
</tr>
<tr>
<td>(0.055, 1.476)</td>
<td>(0.035, 1.589)</td>
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</tbody>
</table>

Values are expressed as mean±SD, except for the glomerular arteriolar resistance and the ultrafiltration coefficient, which are shown as the mean followed in parentheses by the minimum and maximum values. GFR, glomerular filtration rate; Ccr, creatinine clearance; DTPA, diethylenetriaminepentaacetic acid; $P_{GC}$, glomerular capillary pressure; $R_A$, resistance of afferent arterioles; $R_E$, resistance of efferent arterioles; $K_f$, whole-kidney ultrafiltration coefficient.
correlated significantly with that calculated with the 99mTc-DTPA-derived GFR (N = 27, r = .95, p < .001).

**Discussion**

We showed a linear relationship between each pair of mean values for $P_{GC}$, $R_A$, $R_E$, and $K_f$ calculated using the Ccr-derived and 99mTc-DTPA-derived GFRs.

The method used in this study for the clinical investigation of glomerular hemodynamics has been described elsewhere (6, 7) and has been examined carefully (8, 17, 18).

The renal clearance of inulin, which is filtered but is neither reabsorbed nor secreted, represents the absolute GFR. The inulin clearance is the gold standard for GFR. However, in Japan, inulin clearance is not a practical technique for clinical studies, because inulin is not available for routine clinical use. Radioactive agents such as 125I-iothalamate and 99mTc-DTPA have been used to measure the GFR. These markers can provide an absolute GFR, but cannot be used repeatedly, since they are both expensive and invasive. If the test is performed only once or twice, the technical accuracy and reliability of the results cannot be corroborated. In contrast, the Ccr test is easy to perform and is reproducible. In our study, Ccr, RPF, and 99mTc-DTPA clearances were examined simultaneously on the last day of the high-salt diet. The Ccr value was confirmed by serial examinations of the 24-h creatinine clearance on the last 3 d of each diet. Since 90% of creatinine is filtered at the glomeruli and 10% is secreted from the tubules, the Ccr overestimates the GFR. Therefore the Ccr accurately establishes relative GFR, but not absolute values.

In the assessment of glomerular hemodynamics, $P_{GC}$ is the sum of $\Delta P_F$, $P_T$, and $I_C$. Among these three parameters, only $I_C$ is affected by the GFR (see eq. 6 and 7). Although the difference between the GFR values using Ccr or 99mTc-DTPA is 19%, the difference between the values of the mean $I_C$
calculated using Ccr or 99mTc-DTPA is only 1.6\% (data not shown). The difference between the mean PGCs calculated with Ccr or 99mTc-DTPA is also small, only 2\%. This is due to the fact that the values for glomerular hemodynamics obtained here, especially the P_GC, depend primarily on the pressure-natriuresis relationship, not the GFR. Although the Ccr does not provide an absolute GFR, the reproducibility of the test was useful for the assessment of glomerular hemodynamics in our study.

In conclusion, we found that the Ccr can be used as a substitute for GFR in the clinical assessment of glomerular hemodynamics.

**Abbreviations**

Ccr, creatinine clearance; P_GC, glomerular capillary hydraulic pressure; GFR, Glomerular filtration rate; DTPA, diethylenetriaminepentaacetic acid; RPF, renal plasma flow; NIDDM, non-insulin-dependent diabetes mellitus; CGN, chronic glomerulonephritis; MAP, mean arterial pressure; TP, plasma total protein concentration; \( \Delta P_F \), effective filtration pressure; \( P_T \), hydraulic pressure in Bowman’s space; \( \Pi_G \), mean oncotic pressure with glomerular capillaries; \( C_M \), mean concentration of protein in plasma of glomerular capillaries; FF, filtration fraction; \( R_A \), resistance of afferent arterioles; \( R_E \), resistance of efferent arterioles.

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**References**