Table 2. Prevalence of hyperfiltration/hypofiltration according to the stages of prediabetes and prehypertension in all the subjects ($N = 99\ 140$)

	Normal filtration ($n = 87\ 251$)	Hyperfiltration ($n = 5548$)				Hypofiltration ($n = 6341$)			
	n	*n* (%)	Adjusted OR[a] (95% CI[a])	Fully adjusted OR[b] (95% CI[b])	P for trend[b]	*n* (%)	Adjusted OR[a] (95% CI[a])	Fully adjusted OR[b] (95% CI[b])	P for trend[b]
Stages of prediabetes					<0.001				0.813
No prediabetes (FPG <100 mg/dL)	64 566	3525 (4.9%)	1 (reference)	1 (reference)		4384 (6.1%)	1 (reference)	1 (reference)	
Stage 1 prediabetes (FPG 100-109 mg/dL)	12 024	787 (5.7%)	1.22 (1.12–1.32)	**1.29** (1.17–1.41)		960 (7.0%)	1.01 (0.94–1.09)	0.89 (0.82–0.97)	
Stage 2 prediabetes (FPG 110-125 mg/dL)	4938	408 (7.1%)	1.53 (1.37–1.71)	**1.58** (1.38–1.80)		388 (6.8%)	0.95 (0.85–1.06)	0.77 (0.68–0.88)	
Diabetes (FPG ≥126 mg/dL or under treatment)	5723	828 (11.6%)	2.81 (2.58–3.06)	**2.47** (2.22–2.75)		609 (8.5%)	1.19 (1.08–1.30)	**1.18** (1.05–1.33)	
Stages of prehypertension					<0.001				0.044
No prehypertension (BP <120/80 mmHg)	32 757	1902 (5.2%)	1 (reference)	1 (reference)		1890 (5.2%)	1 (reference)	1 (reference)	
Stage 1 prehypertension (BP 120-129/80-84 mmHg)	17 542	1036 (5.3%)	1.01 (0.93–1.09)	1.10 (1.00–1.20)		1036 (5.3%)	0.99 (0.91–1.07)	0.90 (0.82–0.98)	
Stage 2 prehypertension (BP 130-139/85-89 mmHg)	14 689	999 (6.0%)	1.16 (1.07–1.26)	**1.33** (1.21–1.47)		975 (5.9%)	1.07 (0.99–1.16)	0.91 (0.83–1.01)	
Hypertension (BP ≥140/90 mmHg or under treatment)	22 263	1611 (6.1%)	1.26 (1.16–1.36)	**1.52** (1.38–1.68)		2440 (9.3%)	1.45 (1.35–1.56)	**1.12** (1.02–1.22)	

[a]Adjusted for age and sex.
[b]Adjusted for age, sex, body mass index, high-density lipoprotein (HDL-C), lipid-lowering medication use, uric acid and smoking status; the analyses of stages of prediabetes were also adjusted for systolic BP and anti-hypertensive medication use, while analyses of stages of prehypertension were also adjusted for FPG and glucose-lowering medication use. Bold style represents ORs which showed significant results in both adjustments. CI, confidence interval. Hyperfiltration was defined as an eGFR over the age- and sex-specific 95th percentile and hypofiltration was defined as an eGFR below the 5th percentile as shown in Figure 1.

kidney damage, although glomerular hyperfiltration precedes the development of microalbuminuria [22]. Another limitation is that among diabetic subjects with normal filtration, subjects with renal damage who have already undergone hyperfiltration stage might be included in accordance with the hyperfiltration hypothesis [5], though this mixture does not affect the association between prediabetes and hyperfiltration. Since these results were obtained in a Japanese population, confirmation in other ethnic groups is needed.

Our findings should be considered descriptive rather than pathogenetic because we lack longitudinal data on GFR and information on microalbuminuria. Though we believe treating hyperglycemia and high BP from an early and reversible stage as hyperfiltration is important to prevent kidney damage, further confirmation by longitudinal studies is needed. Also, whether age-specific reference values reflect the risk of ESRD, cardiovascular disease or mortality should be proved by prospective studies.

In conclusion, we found that the prevalence of hyperfiltration increased with increasing stage (i.e. worsening) of prediabetes and prehypertension. Kidney function should be monitored in subjects with prediabetes or prehypertension. In people with hyperfiltration, we suggest that hyperglycemia and high BP should be treated as early as possible to prevent the development of kidney damage.

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Conflict of interest statement. None declared.

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AJKD
Original Investigation

GFR Estimation Using Standardized Serum Cystatin C in Japan

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Background: Recently, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) developed glomerular filtration rate (GFR)-estimating equations based on standardized serum cystatin C (CKD-EPI$_{cys}$) and standardized serum creatinine plus standardized serum cystatin C (CKD-EPI$_{cr\text{-}cys}$). We developed new GFR-estimating equations based on standardized cystatin C for a Japanese population and compared their accuracy with the CKD-EPI equations.

Study Design: Accuracy of diagnostic test study.

Setting & Participants: 413 (development data set) and 350 individuals (validation data set).

Index Test: CKD-EPI$_{cys}$; CKD-EPI$_{cr\text{-}cys}$; modifications to CKD-EPI$_{cys}$ and CKD-EPI$_{cr\text{-}cys}$ using Japanese coefficients; and newly developed Japanese eGFR equations based on standardized serum cystatin C (Eq$_{cys}$), cystatin C with a nonrenal factor reflecting hypothesized extrarenal elimination (Eq$_{cys+nonrenal}$), and creatinine in combination with cystatin C (Eq$_{cr\text{-}cys}$). Standardized cystatin C values were determined by a colloidal gold immunoassay traceable to the international certified reference material ERM-DA471/IFCC.

Reference Test: Measured GFR by inulin renal clearance.

Results: In a development data set, we calculated Japanese coefficients for CKD-EPI$_{cys}$ and CKD-EPI$_{cr\text{-}cys}$ of 0.977 (95% CI, 0.853-1.002) and 0.908 (95% CI, 0.889-0.928), respectively. In a validation data set, we compared CKD-EPI$_{cys}$, Eq$_{cys}$, and Eq$_{cys+nonrenal}$ with each other. Bias and accuracy were not significantly different among the 3 equations. The precision of CKD-EPI$_{cys}$ was significantly better than for Eq$_{cys}$ ($P = 0.007$) and not significantly different from Eq$_{cys+nonrenal}$ ($P = 0.6$). We then compared 0.908 × CKD-EPI$_{cr\text{-}cys}$, Eq$_{cr\text{-}cys}$, and Eq$_{average}$ (the average value of Eq$_{cr}$ [previous Japanese equation based on standardized serum creatinine] and Eq$_{cys+nonrenal}$) with each other in the validation data set. Bias and accuracy were not significantly different among the 3 equations. The precision of 0.908 × CKD-EPI$_{cr\text{-}cys}$ was significantly better than for Eq$_{cr\text{-}cys}$ ($P = 0.004$) and not significantly different from Eq$_{average}$ ($P = 0.06$).

Limitations: Limited number of participants with measured GFR >90 mL/min/1.73 m^2. Extrarenal elimination of cystatin C was not measured.

Conclusions: CKD-EPI$_{cys}$ performed well in Japanese individuals, suggesting that equations based on serum cystatin C could be used in patients with different races without modification. Accounting for extrarenal elimination of cystatin C may improve the performance of estimating equations.

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INDEX WORDS: Cystatin C; glomerular filtration rate estimating equation; creatinine; Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).

Glomerular filtration rate (GFR) calculated by the clearance of exogenous markers such as inulin is accurate, but the procedure takes considerable time. As an alternative, GFR-estimating equations have been recommended in clinical practice.[1] Equations based on standardized serum creatinine (SCr), such as the Modification of Diet in Renal Disease (MDRD) Study equation[2] or the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation,[3] have been used most commonly worldwide. Serum cystatin C (SCysC) is a potential alternative GFR marker. GFR-estimating equations based on SCysC level have been developed previously.[4-7] However, most of the equations were based on nonstandardized SCysC values, such that different assay methods may result in different estimated GFRs (eGFRs) being calculated. The International Federation for Clinical Chemists (IFCC) prepared ERM-DA471/IFCC, a primary reference material for cystatin C.[8] Recently, a standardized assay of cystatin C traceable to that reference material has been made available. CKD-EPI developed new equations based on standardized SCysC and SCysC in combination with standardized SCr.[9] In the present

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study, we developed new eGFR equations based on standardized SCysC and SCysC in combination with SCr level in Japanese individuals. We compared their accuracy with the CKD-EPI equations.

METHODS

Participants

We used the same data sets from which the SCr-based Japanese eGFR equation was developed and validated.[10] Details for the individuals have been reported previously.[10,11] Briefly, 763 Japanese patients in 80 medical centers were included. Most were patients with CKD. They were divided into a development (413 individuals) and a validation data set (350 individuals). New equations were obtained from the development data set.

Measurements

Measured GFR (mGFR) was determined using an inulin renal clearance method that has been reported previously.[10] SCr and SCysC levels of 763 individuals were measured at the same time by a single laboratory from December 2006 to July 2007. SCr was measured by an isotope-dilution mass spectrometry–traceable enzymatic method that has been reported previously.[10] SCysC was measured by nephelometric immunoassay (Siemens, Dade Behring, www.siemens.com). In 2006-2007, SCysC measurement was not standardized. In 2011, the standardized method of cystatin C measurement traceable to ERM-DA471/IFCC became available. A project team for verification of immunoassay standardization for SCysC from the Japan Society of Clinical Chemistry, including investigators from 15 manufacturers, analyzed the performance of the 15 SCysC immunoassays available in Japan. Transfer factors from ERM-DA471/IFCC to calibrators of the participating immunoassays were obtained.[12] Standardization was achieved among most of the assays. Further improvement and development were needed for precision and accuracy in the performance of a few immunoassays.[12] The colloidal gold immunoassay (Alfresa Pharma, www.alfresa-pharma.co.jp) is one of the immunoassays in which standardization was achieved. In the present study, SCysC values of 727 frozen samples were remeasured by this colloidal gold immunoassay, which was traceable to ERM-DA471/IFCC. SCysC values of the remaining 36 of the 763 samples were calibrated to the standardized value using the regression model obtained from the 727 samples.

Index Tests

Extant Equations

We used the previously published Japanese eGFR equation based on standardized SCr (Eq_{cr}),[10] as well as the CKD-EPI equations for standardized SCysC[9]: $CKD\text{-}EPI_{cys}$ and $CKD\text{-}EPI_{cr\text{-}cys}$.

Coefficient-Modified Equations for the Japanese Population

Coefficients appropriate for a Japanese population were calculated in the development data set for use in the CKD-EPI equations. The coefficients were determined by minimizing the sum of squared errors between eGFR and mGFR.

Development of New eGFR Equations

An equation based on standardized SCysC (Eq_{cys}) was derived from 413 individuals. We made a multiple linear regression model with the variables age, sex, and SCysC level in relation to mGFR (in milliliters per minute per 1.73 m^2). SCysC and mGFR were log transformed. The multiple linear regression model is $\ln(eGFR) = A \times \ln(SCysC) + C \times Age + D \times Female + E$, where A, C, and D are the coefficients for the variables and E is the intercept.

An equation based on standardized SCysC and SCr ($Eq_{cr\text{-}cys}$) was developed from 413 individuals. The multiple linear regression model is $\ln(eGFR) = A \times \ln(SCysC) + B \times \ln(SCr) + C \times Age + D \times Female + E$, where A, B, C, and D are coefficients for the variables and E is the intercept.

In individuals with wide-ranging mGFRs, we previously reported that the relationship between SCr and SCysC levels was not linear.[13] As opposed to SCr, SCysC level did not increase in association with a decrease in mGFR in individuals with very low mGFRs. A plot of the regression line of 1/SCysC versus mGFR gave a significantly negative intercept of approximately −8 mL/min/1.73 m^2.[13] Therefore, we hypothesized a constant extrarenal elimination of SCysC of 8 mL/min/1.73 m^2 and developed an equation based on standardized SCysC with a constant nonrenal factor of 8 mL/min/1.73 m^2 ($Eq_{cys+nonrenal}$). The multiple linear regression model is as follows: $\ln(eGFR + 8) = A \times \ln(SCysC) + C \times Age + D \times Female + E$, where A, C, and D are the coefficients for the variables and E is the intercept.

Validation of the Equations

We compared the accuracy and differences between mGFR and eGFR among equations based on SCr (Eq_{cr}) and SCysC ($CKD\text{-}EPI_{cys}$, Eq_{cys}, and $Eq_{cys+nonrenal}$) levels and equations based on SCr and SCysC levels together ($CKD\text{-}EPI_{cr\text{-}cys}$, coefficient-modified $CKD\text{-}EPI_{cr\text{-}cys}$, and $Eq_{cr\text{-}cys}$) using a validation data set. We also examined the average value of Eq_{cr} and $Eq_{cys+nonrenal}$ ($Eq_{average}$).

Statistical Analysis

Bias was expressed as mean ± standard deviation or median and interquartile range of the difference between mGFR and eGFR (mGFR − eGFR). Precision was evaluated by the absolute value of the difference between mGFR and eGFR. Precision was evaluated by paired t test. The accuracy of the equation was expressed as the percentage of individuals with eGFR within ±20% (P_{20}) and ±30% (P_{30}) of mGFR. Accuracy was evaluated by χ^2 tests.

Table 1. Clinical Characteristics of the Study Population

Characteristic	Development Data Set	Validation	*P*
No.	413	350	—
Male sex	262 (63)	203 (58)	0.1
Age (y)	51.4 ± 16.5	53.9 ± 17.5	0.04
Height (cm)	163.2 ± 8.8	161.6 ± 9.5	0.01
Weight (kg)	61.0 ± 12.9	60.4 ± 12.7	0.5
BSA (m^2)	1.65 ± 0.19	1.63 ± 0.19	0.2
BMI (kg/m^2)	22.8 ± 3.8	23.0 ± 3.8	0.4
Diabetes	82 (20)	77 (22)	0.5
Hypertension	235 (57)	202 (58)	0.8
Transplant	9 (2)	2 (1)	0.06
Kidney donor	1 (0)	10 (3)	0.003
SCr (mg/dL)	1.62 ± 1.59	1.57 ± 1.38	0.6
SCysC (mg/L)	1.72 ± 1.09	1.70 ± 1.00	0.8
mGFR (mL/min/1.73 m^2)	59.1 ± 35.4	57.2 ± 34.7	0.5

Note: Continuous data are expressed as mean ± standard deviation; categorical data, as number (percentage).

Abbreviations: BMI, body mass index; BSA, body surface area; mGFR: measured glomerular filtration rate; SCr, serum creatinine; SCysC, serum cystatin C.

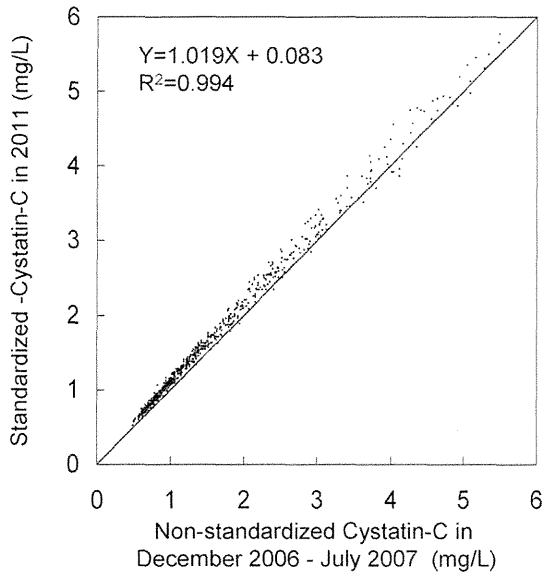

Figure 1. Relationship between standardized cystatin C values by a colloidal gold immunoassay (Alfresa Pharma) in 2011 and the values by nephelometric immunoassay (Siemens, Dade Behring) in 2006 and 2007. Solid line represents the line of identity.

Statview, version 4.02 (SAS Institute, www.sas.com), and JMP, version 8.01 (SAS Institute), were used for statistical analysis. Smoothed lines fit to the data were calculated using a spline model of Stone-Koo of JMP version 8.01 with $\lambda = 10{,}000$ in the software.

RESULTS

GFR-estimating equations and a coefficient to modify the CKD-EPI equations for Japanese were developed from 413 participants and validated using 350 participants. Clinical characteristics of participants are listed in Table 1. Standardized SCysC values measured in 2011 were compared with the previous (nonstandardized) values measured in 2006 and 2007 using 727 samples (Fig 1). R^2 value was 0.994. Mean SCysC level in 2011 was 1.60 mg/L, whereas that in 2006-2007 was 1.71 mg/L. A regression model showed an intercept of 0.083 (95% confidence interval [CI], 0.072-0.094) and slope of 1.019 (95% CI, 1.014-1.025), indicating that the previously measured SCysC values by nephelometric immunoassay were significantly lower than the standardized values measured by a colloidal gold immunoassay.

The coefficients to modify CKD-EPI$_{cys}$ and CKD-EPI$_{cr\text{-}cys}$ for a Japanese population, calculated from a development data set of 413 participants, were 0.977 (95% CI, 0.853-1.002) and 0.908 (95% CI, 0.889-0.928), respectively. We used 0.908 to modify the CKD-EPI$_{cr\text{-}cys}$ for Japanese because the coefficient was significantly different from 1.0. New equations were obtained from the development data set. Results of the multiple linear regression models are listed in Table 2. The mean mGFR of 350 individuals was 57 ± 35 mL/min/1.73 m^2. eGFRs calculated by the CKD-EPI$_{cys}$, CKD-EPI$_{cr\text{-}cys}$, 0.908 × CKD-EPI$_{cr\text{-}cys}$, Eq$_{cr}$, Eq$_{cys}$, Eq$_{cr\text{-}cys}$, Eq$_{cys+nonrenal}$, and Eq$_{average}$ were 57 ± 34, 62 ± 36, 57 ± 32, 55 ± 32, 56 ± 34, 56 ± 33, 55 ± 32, and 55 ± 31 mL/min/1.73 m^2, respectively.

We compared the performances of Eq$_{cys}$, Eq$_{cys+nonrenal}$, and CKD-EPI$_{cys}$ with each other (Table 3). Bias was not significantly different among the 3 equations. The precision of CKD-EPI$_{cys}$ was significantly better than for Eq$_{cys}$ ($P = 0.007$) and not significantly different from Eq$_{cys+nonrenal}$ ($P = 0.6$). The precision of Eq$_{cys+nonrenal}$ was significantly better than for Eq$_{cys}$ ($P < 0.001$). Accuracy was not significantly different among the 3 equations.

Next we compared the performance of Eq$_{cr\text{-}cys}$, Eq$_{average}$, and 0.908 × CKD-EPI$_{cr\text{-}cys}$ with each other (Table 3). Bias was not significantly different among the 3 equations. The precision of 0.908 × CKD-EPI$_{cr\text{-}cys}$ was significantly better than for Eq$_{cr\text{-}cys}$ ($P = 0.004$) and not significantly different from Eq$_{average}$ ($P = 0.06$). The precision of Eq$_{average}$ was significantly better than for Eq$_{cr\text{-}cys}$ ($P = 0.04$). Accuracy was not significantly different among the 3 equations.

Figure 2 shows the bias (mGFR − eGFR) versus eGFR of CKD-EPI$_{cys}$, 0.908 × CKD-EPI$_{cr\text{-}cys}$, Eq$_{cys+nonrenal}$, and Eq$_{average}$ for all 763 individuals. Mean biases of CKD-EPI$_{cys}$, 0.908 × CKD-EPI$_{cr\text{-}cys}$, Eq$_{cys+nonrenal}$, and Eq$_{average}$ were 0.3 ± 17.1, 0.5 ± 15.3, 1.9 ± 16.9, and 1.9 ± 15.7 mL/min/1.73 m^2, respectively. The systemic bias of eGFR was small in all equations. The smoothed lines show the fit of the data. The smoothed lines of CKD-EPI$_{cys}$ and Eq$_{cys+nonrenal}$ were upwardly curving. Individuals with eGFR of ~50 mL/min/1.73 m^2 seemed to have underestimated GFRs compared with individuals with eGFR >100 mL/min/1.73 m^2.

DISCUSSION

The MDRD Study equation and SCr-based CKD-EPI equation have compensation coefficients of 1.212 and 1.159, respectively, for a black population.[2,3] Both equations overestimate GFR in Japanese individuals, and the Japanese coefficients for the MDRD Study and SCr-based CKD-EPI equations have been calculated as 0.808 and 0.813, respectively.[10,11] SCr levels are affected by several factors other than GFR, including muscle mass. Variation in creatinine generation due to age, sex, race, and clinical conditions influences SCr levels. These results suggest that it may be difficult to develop a single SCr-based eGFR equation for estimating GFR in different ethnic groups. SCysC is influenced less by surrogates of muscle mass, including age, sex, and race.[14] In this study, we found that the ethnic coefficient for CKD-EPI$_{cys}$ in a

Table 2. Coefficients of Models Obtained From the Development Data Set

Model	Variables					Coefficient for Japanese
	A (log[SCysC])	B (log[SCr])	C (Age)	D (Female)	E (intercept)	
Eq_{cr}		−1.094 (−1.139 to −1.048)	−0.287[a] (−0.366 to −0.208)	−0.302 (−0.364 to −0.241)	5.267 (4.961 to 5.573)	
CKD-EPI_{cys}	−1.328 if SCysC >0.8; −0.499 if SCysC <0.8		−0.004	−0.07	4.594 if SCysC >0.8; 4.779 if SCysC <0.8	0.977 (0.853 to 1.002)
CKD-EPI_{cr-cys}	−0.711 if SCysC >0.8; −0.375 if SCysC <0.8	−0.601 if SCr >0.9 (♂) or >0.7 (♀);−0.207 if SCr <0.9 (♂);−0.248 if SCr<0.7 (♀)	−0.005	−0.189 if SCr >0.7; ND if SCr <0.7	4.683 if SCysC >0.8 and SCr >0.9 (♂) or >0.7 (♀); 4.758 if SCysC <0.8 and SCr >0.9 (♂) or SCr >0.7 (♀); 4.725 if SCysC >0.8 and SCr <0.9 (♂); 4.800 if SCysC <0.8 and SCr <0.9 (♂); 4.620 if SCysC >0.8 and SCr <0.7 (♀); 4.695 if SCysC <0.8 and SCr <0.7 (♀)	0.908 (0.889 to −0.928)
Eq_{cys}[b]	−1.324 (−1.385 to −1.263)		−0.0039 (−0.0059 to −0.0019)	−0.112 (−0.177 to −0.048)	4.642 (4.562 to 4.722)	
Eq_{cr-cys}[c]	−0.575 (−0.693 to −0.457)	−0.670 (−0.766 to −0.571)	−0.0049 (−0.0065 to −0.0032)	−0.243 (−0.300 to −0.186)	4.518 (4.431 to 4.605)	
$Eq_{cys+nonrenal}$[d]	−1.019 (−1.065 to −0.973)		−0.0038 (−0.0053 to −0.0023)	−0.073 (−0.122 to −0.024)	4.642 (4.562 to 4.722)	

Note: Values shown in parentheses are 95% confidence intervals.

Abbreviations and definitions: CKD-EPI_{cr-cys}, standardized SCr- and SCysC–based Chronic Kidney Disease Epidemiology Collaboration equation; CKD-EPI_{cys}, standardized SCysC-based Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; Eq_{cr}, Japanese equation based on standardized SCr; Eq_{cr-cys}, Japanese equation based on standardized SCr in combination with SCysC; Eq_{cys}, Japanese equation based on standardized SCysC; $Eq_{cys+nonrenal}$, Japanese equation based on standardized SCysC with a nonrenal factor reflecting hypothesized extrarenal elimination; SCysC, standardized serum cystatin C (in mg/L); ND, not determined because of different equations between male and female; SCr, standardized serum creatinine (in mg/dL).

[a]Coefficient was calculated for log(age).

[b]Final equation for Eq_{cys}: eGFR (mL/min/1.73 m^2) = $96 \times SCysC^{-1.324} \times 0.996^{Age} \times 0.894$ (if female).

[c]Final equation for Eq_{cr-cys}: eGFR (mL/min/1.73 m^2) = $92 \times SCysC^{-0.575} \times SCr^{-0.670} \times 0.995^{Age} \times 0.784$ (if female).

[d]Final equation for $Eq_{cys+nonrenal}$: eGFR (mL/min/1.73 m^2) = $\{104 \times SCysC^{-1.019} \times 0.996^{Age} \times 0.929$ (if female)$\} - 8$.

Table 3. Performance of Equations in Validation Data Set

Model	RMSE (95% CI)	Bias Median (95% CI), IQR	Precision[a] Median (95% CI), IQR	Accuracy (%) P_{20} (95% CI)	Accuracy (%) P_{30} (95% CI)
CKD-EPI$_{cys}$	0.31 (0.27 to 0.35)	−1.1 (−1.9 to 0.9), 14.5	7.3 (6.3 to 8.4), 10.9	60 (55 to 65)	79 (74 to 83)
CKD-EPI$_{cr\text{-}cys}$	0.31 (0.26 to 0.35)	−4.7 (−5.7 to −3.1), 13.2	7.3 (6.5 to 8.5), 11.3	60 (55 to 65)	77 (72 to 81)
0.908 × CKD-EPI$_{cr\text{-}cys}$	0.29 (0.24 to 0.33)	0.3 (−0.6 to 1.2), 11.6	5.8 (5.1 to 6.6), 10.4	67 (62 to 72)	82 (78 to 86)
Eq$_{cr}$	0.32 (0.28 to 0.36)	1.9 (0.9 to 3.2), 14.9	7.4 (6.2 to 8.4), 13.2	59 (54 to 64)	75 (70 to 79)
Eq$_{cys}$	0.32 (0.28 to 0.36)	0.9 (−0.6 to 2.5), 14.8	7.3 (6.4 to 8.3), 11.7	58 (53 to 63)	77 (72 to 81)
Eq$_{cr\text{-}cys}$	0.30 (0.25 to 0.34)	1.1 (0.2 to 2.4), 12.0	6.2 (5.6 to 7.0), 9.9	65 (60 to 70)	81 (77 to 85)
Eq$_{cys+nonrenal}$	0.31 (0.27 to 0.35)	0.3 (−1.2 to 1.9), 14.8	6.7(5.9 to 8.0), 10.3	60 (55 to 65)	78 (73 to 82)
Eq$_{average}$	0.29 (0.24 to 0.33)	1.1 (−0.2 to 2.2), 11.7	6.1 (5.5 to 6.8), 9.3	66 (61 to 71)	82 (78 to 86)

Abbreviations and definitions: bias (in mL/min/1.73 m^2), difference between mGFR and eGFR (ie, mGFR − eGFR); CI, confidence interval; CKD-EPI$_{cys}$, standardized serum cystatin C–based Chronic Kidney Disease Epidemiology Collaboration equation; CKD-EPI$_{cr\text{-}cys}$, standardized serum creatinine and cystatin C–based Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; Eq$_{average}$, average of Eq$_{cr}$ and Eq$_{cys+nonrenal}$; Eq$_{cr}$, Japanese equation based on standardized serum creatinine; Eq$_{cr\text{-}cys}$, Japanese equation based on standardized serum creatinine in combination with cystatin C; Eq$_{cys}$, Japanese equation based on standardized serum cystatin; Eq$_{cys+nonrenal}$, Japanese equation based on standardized serum cystatin C with a nonrenal factor reflecting hypothesized extrarenal elimination; IQR, interquartile range; mGFR, measured glomerular filtration rate; P_x, percentage of eGFR within x% of mGFR; precision (in mL/min/1.73 m^2), absolute value of the difference between mGFR and eGFR; RMSE, root mean square error.

[a] $P = 0.007$ and $P = 0.6$, respectively, for Eq$_{cys}$ and Eq$_{cys+nonrenal}$ versus CKD-EPI$_{cys}$. $P = 0.004$ and $P = 0.06$, respectively, for Eq$_{cr\text{-}cys}$ and Eq$_{average}$ versus CKD-EPI$_{cr\text{-}cys}$.

Japanese population was 0.977 (95% CI, 0.853-1.002), which is close to 1.0, suggesting the possibility that equations based on SCysC level may be more accurate than equations based on SCr level in patients of different races or clinical conditions that have variation in creatinine generation.

The performance of CKD-EPI$_{cys}$ was better than that of Eq$_{cys}$ (Table 3). The precision of CKD-EPI$_{cys}$ was significantly better than for Eq$_{cys}$. The higher precision may be due to the model of CKD-EPI$_{cys}$. CKD-EPI$_{cys}$ uses a 2-slope linear spline with a knot to model the relationship between log(mGFR) and log(SCysC). The 2-slope spline has a steeper slope of GFR versus SCysC at cystatin C levels >0.8 mg/L and a less steep slope at SCysC levels <0.8 mg/L. The significantly better performance of Eq$_{cys+nonrenal}$ compared with Eq$_{cys}$ suggests that accounting for extrarenal elimination of SCysC may improve equation performance. However, Eq$_{cys+nonrenal}$ did not perform better than CKD-EPI$_{cys}$.

We observed that CKD-EPI$_{cr\text{-}cys}$ overestimates GFR in Japanese individuals because the equation is based on not only SCysC level, but also SCr level. The ethnic coefficient for CKD-EPI$_{cr\text{-}cys}$ in Japanese was 0.908 (95% CI, 0.889-0.928). The coefficient-modified CKD-EPI$_{cr\text{-}cys}$ showed good performance in Japanese (Table 3). The precision of 0.908 × CKD-EPI$_{cr\text{-}cys}$ was significantly better than for Eq$_{cr\text{-}cys}$. The explanation for the higher precision of 0.908 × CKD-EPI$_{cr\text{-}cys}$ may be the use of 2-slope linear splines to model the relationships between log(mGFR) and log(SCr) and log(SCysC).

It has been suggested that a GFR-prediction equation using the average of GFR estimations obtained from an SCr and SCysC–based prediction equation is a good innovation.[15-18] The advantages of using the average of GFR estimations include not only better diagnostic performance, but also the inherent possibility of comparing the 2 estimates and thereby the possibility to exclude the influence of nonrenal factors on the final GFR estimate.[17,18] When the discrepancy between eGFR based on SCysC level and eGFR based on SCr level is large, we should consider clinical conditions influencing SCr, such as the presence of abnormal muscle mass or factors affecting SCysC. For the latter, it has been reported that SCysC levels are influenced by thyroid function[19,20] and glucocorticoid and immunosuppressant therapy.[21]

There are a number of limitations inherent to our study. Participants were almost exclusively patients with native kidney disease, and there was a limited number of individuals with mGFR >90 mL/min/1.73 m^2. Extrarenal elimination of SCysC was not measured. The performance of the equations in healthy individuals should be evaluated. The validation data set has been used before in a previous study[10,11]; thus, in a sense, we have already "looked" at the validation data before using it in the present study.

In summary, CKD-EPI$_{cys}$ showed good performance in Japanese. The Japanese ethnic coefficient of CKD-EPI$_{cys}$ was about 1.0, suggesting the possibility that equations based on SCysC level could be used without modification in patients with different races or clinical conditions that have variation of creatinine

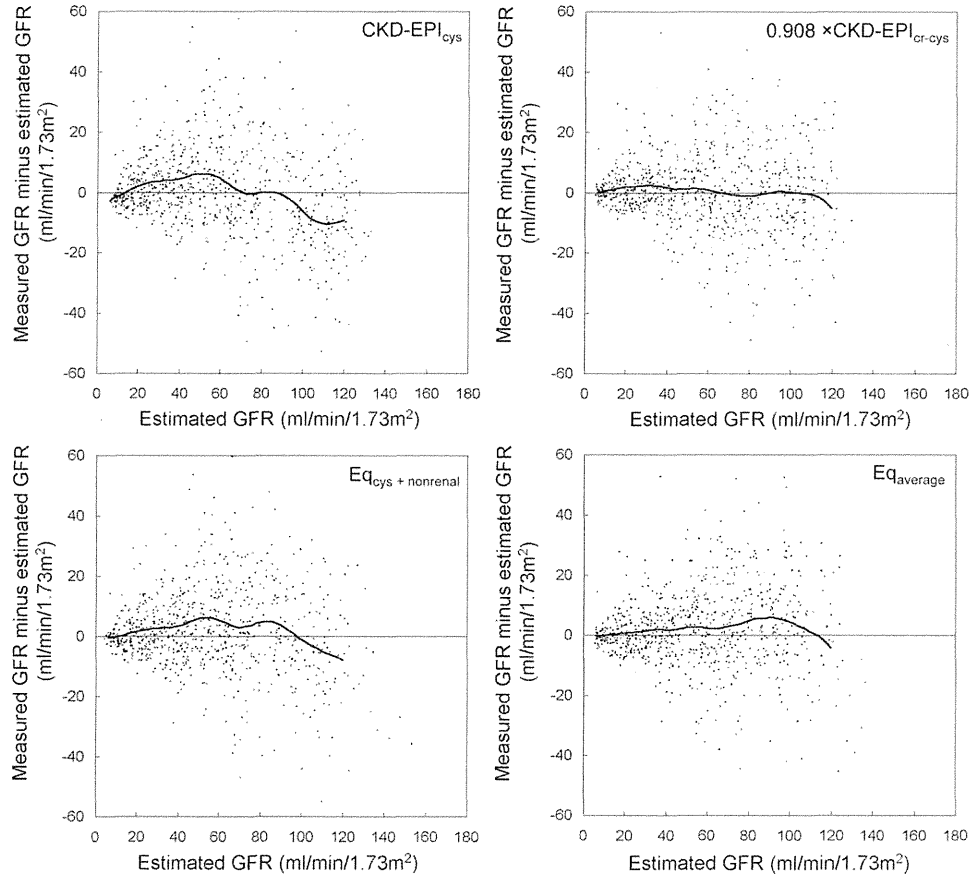

Figure 2. Relationship between estimated glomerular filtration rate (GFR) and bias (calculated as measured GFR − estimated GFR) in all study participants. Solid horizontal line indicates no difference. Smoothed line shows the fit of the data. Abbreviations: CKD-EPI$_{cys}$, standardized serum cystatin C–based Chronic Kidney Disease Epidemiology Collaboration equation; CKD-EPI$_{cr-cys}$, standardized serum creatinine and cystatin C–based Chronic Kidney Disease Epidemiology Collaboration equation; Eq$_{average}$, average value of Eq$_{cr}$ [Japanese equation based on standardized serum creatinine] and Eq$_{cys+nonrenal}$; Eq$_{cys+nonrenal}$, Japanese equation based on standardized serum cystatin C with a nonrenal factor reflecting hypothesized extrarenal elimination.

generation. The precision of CKD-EPI$_{cys}$ was significantly better compared with Eq$_{cys}$, suggesting that a 2-slope linear spline with a knot to model the relationship between log(mGFR) and log(SCysC) improves the precision of the GFR estimation. Eq$_{cys+nonrenal}$ also showed significantly better performance compared with Eq$_{cys}$, suggesting that accounting for extrarenal elimination may improve the performance of equations based on SCysC level.

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Editorial

慢性腎臓病この10年と今後の展望

槇野　博史

〔日内会誌　101：1233～1235，2012〕

Key words　慢性腎臓病，eGFR（推算GFR），アルブミン尿，慢性腎臓病対策協議会

2002年に米国の腎臓財団から慢性腎臓病（CKD）の概念が提唱され丁度10年が過ぎた．まず，この10年を振り返り，今後のCKD診療について展望を述べてみたいと思う．

慢性に進行する腎臓の疾患は数多くあり，腎臓の疾患名は解り難いという批判があった．さらに，透析患者は我が国のみならず，世界各地で増加しており，経済的にも問題になっていた．そこでありとあらゆる腎障害（特に蛋白尿が重要），又は血清クレアチニン値から計算した推算GFR（glomerular filtration rate）が60 ml/min/1.73 m^{2}未満である状態が3カ月以上続く場合をCKDと定義された[1]．このCKDという新たな概念は腎臓専門医のための病名ではなくて一般かかりつけ医，コメディカル，国民のための病名である．CKDを人類の健康を脅かす新しい疾病と位置付け，増大する透析患者を抑制することと，CKD患者に高率に合併するCVD（心血管疾患）の予防を目指そうとするものである．

私にとってこれまでの中で最も衝撃的な論文はGoらの，推定GFRが60 ml/min/1.73 m^{2}を切ってくると加速度的にCVDにより生命予後が不良となるものであった[2]．私はそれまでは腎臓内科の最大の治療目標はCKD患者を透析に移行しないようにすることと理解していた．しかし，この論文によりCKDの治療目標はCVDの発症も予防しながら少しでも腎機能を悪化させないという，よりハードルの高いものとなった．従って腎臓専門医にとって，当然ではあるが腎のみならず心・血管病をはじめとする全身の病態の把握が必要になった．また，なぜ腎臓が障害されると動脈硬化が進展してCVDを発症するのか，改めて心腎連関の病態解明が必要となり，その研究が進んできた．

日本腎臓学会では2006年に慢性腎臓病対策委員会を設置して，疫学調査研究，診療システム構築，社会への働きかけ，国際協調・貢献を4つの柱として，総合的にCKD対策を行ってきた[3]．かかりつけ医と腎臓専門医の連携を深めて病診連携を推進するためのツールとして2007年9月に「CKD診療ガイド」を発行した[4]．その後イヌリンクリアランスによりGFRを実測して日本人のGFR推算式が完成し[5]，2009年に改定版を出した[6]．

CKD対策は腎臓専門医のみではとても実践できないので，学際的な協力を得て，行政や社会の協力を得ながら進めて行く必要がある．その為に2006年にまず日本腎臓学会，日本透析医学

岡山大学大学院腎・免疫・内分泌代謝内科学

Chronic Kidney Disease（CKD）—Recent Progress. Editorial：CKD initiative in these 10 years and perspective.

Hirofumi Makino：Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan.

Editorial

会と日本小児腎臓病学会が中心となってCKD対策のヘッドクオーターとして日本CKD対策協議会を立ち上げた．その後日本医師会が正式に参加することとなり，また30を超える学会や団体の協力を得て世界腎臓デー（3月第二木曜日）のイベントをはじめとして医療界や社会への啓発活動を進めている[7]．

また，行政もCKDの重要性を認識し，厚生労働省の戦略研究のテーマとしてCKDが取り上げられた．これは，かかりつけ医/非腎臓専門医と腎臓専門医の協力を促進する慢性腎臓病患者の重症化予防の為の診療システムの有用性を検討する研究（FROM-J）で全国49の医師会で開始されている[8]．成果目標はCKD診療ガイドに沿った治療と病診連携により5年後の透析導入患者数を予測数より15%減少させることであり，その成果が期待されている．

CKDと言う概念はまず一般化することから始まったが，その後，詳細な検証が進んでいる．艮陵CKD研究では原疾患により大きく予後が異なることが明らかになった[9]．即ち原発性腎疾患に比較して高血圧性腎症群，糖尿病性腎症群ではCVDと死亡リスクは有意に高値であった．現在KDIGO（Kidney Disease : Improving Global Outcomes）によるCKD定義の再検討が進んでいる[10]．それによるとまず原疾患を記載することとなっている．今後は原疾患に応じたよりきめ細かいCKD対策が必要になってくる．

アルブミン尿・蛋白尿はeGFRとは独立したCKDの進行因子であることが次々に明らかにされて，CKDの重症度分類としてeGFRとアルブミン尿（蛋白尿）の程度を併記することが決まった．我が国においてアルブミン尿の測定は早期糖尿病性腎症の疑いでしか保険診療上認められておらず，顕性腎症期や他の腎疾患では認められていない．世界のスタンダードであるアルブミン尿をCKD患者に測定可能となるように，行政への働きかけを継続して行く必要がある．

フランスで行われたAVENIRstudy[11]では腎臓内科に紹介されてから透析導入までの治療内容が検討された．その結果RAS抑制薬，重曹補充療法，活性型ビタミンD，スタチンなどのCKDに対する充分な治療が行われていないことが明らかになった．我が国においてもCKDの標準療法を検証し，さらに普及させていく必要がある．現在CKD患者の透析導入基準が再検討されているが，IDEALstudyでは，ガイドラインに従って治療された患者ではeGFRが10 ml/min/1.73 m^{2}で透析導入しても15 ml/min/1.73 m^{2}で導入してもその後の生命予後には有意差が無いことが明らかにされた[12]．すなわち，保存期の治療の重要性が再認識されたわけである．

日本透析医学会の年末調査では透析導入患者数は2009年から減少に転じており，糖尿病性腎症では統計調査を開始して初めて導入患者数が前年に比べて低下した[13]．様々な要因が関与していると考えられるが，その一つの要因としてCKDという概念が定着して，かかりつけ医によるCKD治療の標準化が浸透しつつあるためではないかと考えられる．5年後の透析導入患者数がFROM-Jの目標通りの15%を切れるようにさらにCKD対策を浸透させていく必要がある．

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招請講演

4. 糖尿病性腎症の病態に立脚した治療

槇野　博史

Key words：糖尿病性腎症，糸球体過剰濾過，細胞周期，血管新生，炎症

はじめに

正常耐糖能，耐糖能異常，2型糖尿病へと進展する過程で，膵Langerhans島（ラ氏島）の肥大と細胞増殖と高インスリン血症が初期にもたらされ，その後ラ氏島炎症やアポトーシスによって細胞の減少が進行し最終的にはラ氏島の線維化によってインスリン分泌能の廃絶がもたらされる．その過程はまさしく糖尿病性腎症の進展過程に類似性がある．腎症の初期においては糸球体過剰濾過や糸球体肥大がもたらされ，その後炎症とアポトーシスによって細胞数は減少し，最終的には糸球体硬化と間質の線維化によって末期腎不全に至る（図1）．腎症の研究においてこれらのステージにおける病態を検討し，さらに臨床研究を行ってきた．その結果糸球体過剰濾過と血管新生，細胞肥大と細胞周期，microinflammationの関与を明らかにした（図2）．さらにこれらの複数の病態に対して治療介入を行うにはチーム医療を基盤にした集約的治療が重要であると考え臨床研究を推進している．本講演ではこれら当科のデータを中心に概説した．

1．糸球体の過剰濾過と血管新生

糖尿病性腎症の進行には糸球体過剰濾過が関与しており，その成因として輸入細動脈の拡張が指摘されている．我々は糸球体肥大を血行動態と血管新生の側面から検討してきた．糸球体過剰濾過は糖尿病性腎症の最も早期の変化であるが，輸入細動脈と糸球体毛細血管の拡張には，輸入細動脈内皮細胞や糸球体内皮細胞の，ecNOS（endotherial cell nitric oxide synthase）の発現が上昇して，nitric oxideの産生を増加させることによって血管拡張が引き起こされていることを報告した[1]．さらにadrenomedullinとその受容体の輸入細動脈における発現上昇が血管拡張と糸球体過剰濾過に関与していることを報告した[2]．

血管内皮増殖因子（vascular endothelial growth factor：VEGF）は代表的な血管新生促進因子である．VEGFは腎糸球体足細胞より主とし

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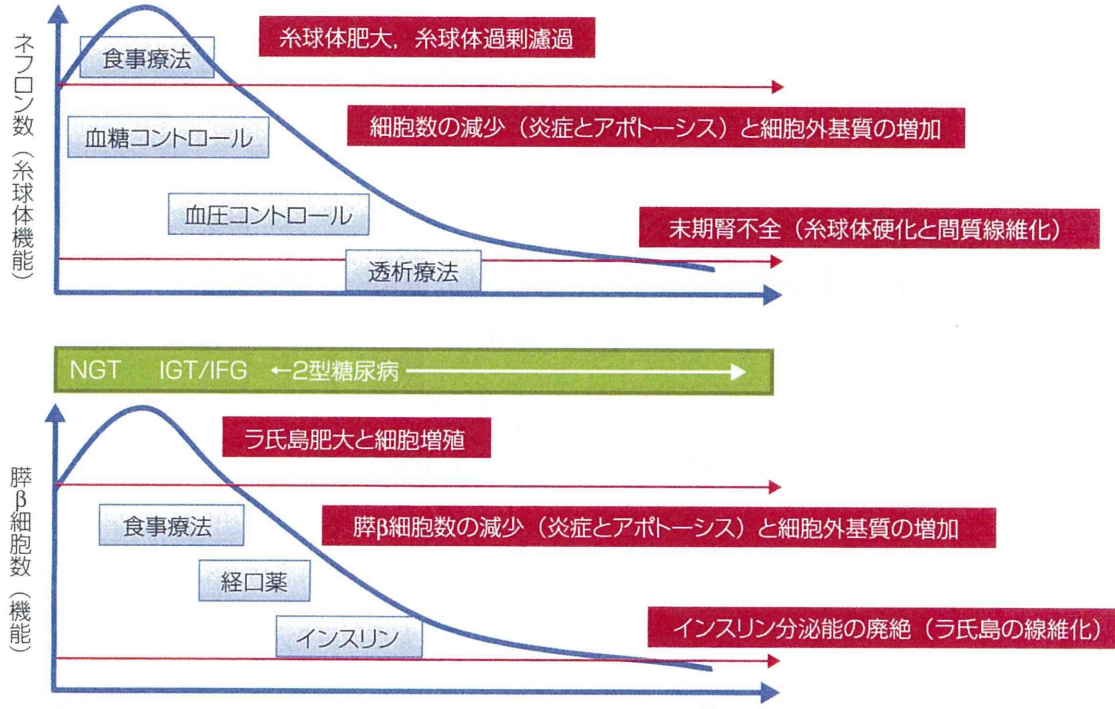

図 1.　2 型糖尿病と糖尿病性腎症進展の類似性

NGT : normal glucose tolerance
IGT : impaired glucose tolerance
IFG : impaired fasting glucose

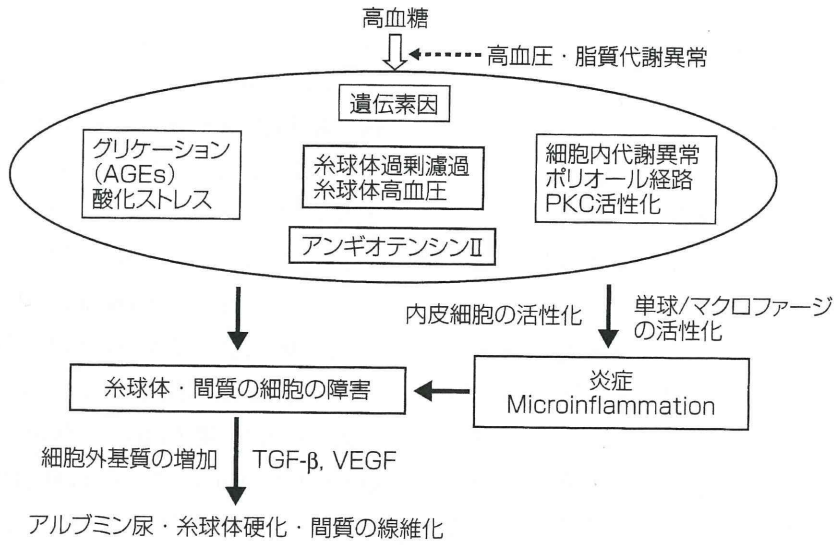

図 2.　糖尿病性腎症の成因と治療標的

て産生され，内皮細胞上の受容体VEGFR-1（vascular endothelial growth factor receptor-1），VEGFR-2 に作用する．糖尿病性腎症モデルにおける抗VEGF療法による糖尿病性腎症の治療効果が示されているが，直接的VEGF阻害薬以外にも，種々の血管新生抑制因子による腎症治療効果を

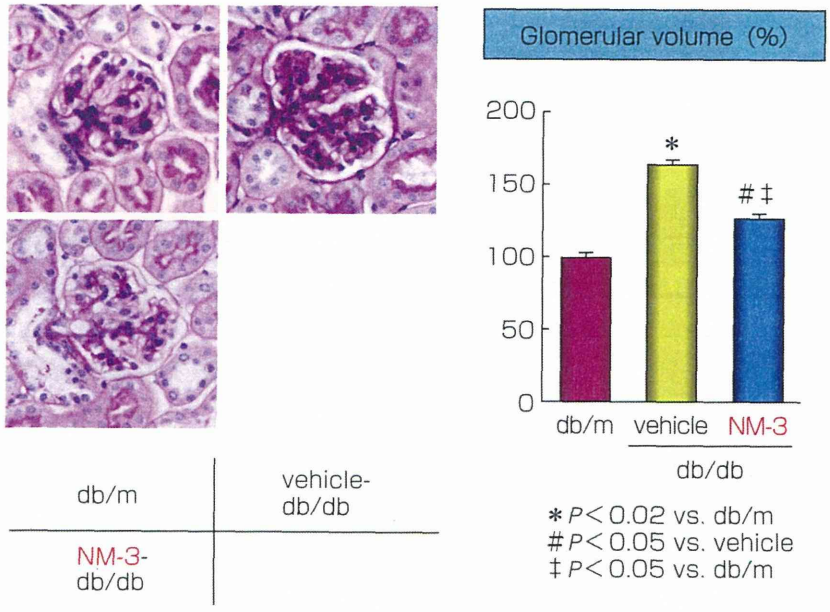

図 3. 血管新生抑制因子による糖尿病性腎症治療効果

報告してきた．当科の前島らは血管新生抑制因子であるtumstatin[3]，endostatin[4]，NM-3[5]の投与によって，糸球体肥大とアルブミン尿が抑制され，血管新生が糖尿病性腎症の発症初期のメカニズムとして重要であることを明らかにした（図 3）．血管内皮細胞をVEGF刺激した際に発現増加する遺伝子の中から血管新生抑制作用を示すvasohibin-1（VASH-1）が東北大学の佐藤らによって新たに同定されたが，VASH-1 はsprouting（発芽）等の活発な血管新生部位では発現が低下し，血管新生終息部位にて発現増加し，血管新生の終息/血管の成熟に関与すると考えられる．当科の前島らは，VASH-1 発現アデノウィルスベクター（AdVASH-1）をSTZ（streptozotocin）誘発 1 型糖尿病モデルマウス並びに 2 型糖尿病モデルであるdb/dbマウスに静脈内投与し，腎症変化の有意な抑制効果を観察した[6,7]．STZ群における腎皮質でのTGF-β（transforming growth factor-β），macrophage chemoattractant-1（MCP-1），receptor for AGE（advanced glycation endoproduct）（RAGE），VEGFR-2 発現増加ならびにリン酸化がAd-hVASH-1 投与群で有意に抑制された．内在性血管新生制御因子VASH-1 を外因性に投与することにより，内皮細胞のみならずメサンギウム細胞への直接作用をも介して血管新生制御・抗線維化・抗炎症・AGE作用抑制等の機序から糖尿病性腎症の進展を制御する可能性が示唆された．

2. 糖尿病性腎症と細胞周期異常

糖尿病性腎症に認められる細胞肥大は，蛋白合成の亢進とG1 期細胞周期停止が関与しており，サイクリンインヒビターである$p21^{Cip1}$，$p27^{Kip1}$の活性化が関与していると指摘されてきている．我々はpioglitazoneをOLETF（Otsuka Long-Evans Tokushima Fatty）ラットに投与したところ，糸球体上皮細胞において増加した$p21^{Cip1}$，$p27^{Kip1}$陽性細胞を減少させ，IV型コラーゲンやTGF-βの発現が減少して，細胞外基質の蓄積やマクロファージの浸潤，そしてアルブミン尿や糸球体肥大が抑制されることを報告した．peroxisome proliferator activated receptor（PPARγ）はメサンギウム細胞さらには糸球体上皮細胞に

発現しており，これらの細胞が作用ターゲットとなっていると考えられる[8]．さらにgalectin-9は，活性化T細胞や胸腺細胞などの細胞にアポトーシスを誘導することが知られており細胞周期制御の調節因子である．そこでdb/dbマウスにgalectin-9リコンビナント蛋白を投与したところ，galectin-9が糖尿病性腎症のG1期における細胞周期停止を正常化して，腎症への治療効果を発揮することを報告した[9]．

3. microinflammationの関与

典型的な炎症性疾患の病態は，発赤・腫脹・疼痛・変形・機能障害を主徴とするものであり，血清学的にはCRP（C-reactive protein）の上昇や赤沈の亢進を伴い，関節リウマチや血管炎などが代表的な炎症性疾患である．これに対して，動脈硬化や糖尿病性腎症に見られる「炎症」は，従来の炎症の概念とは異なり，血管壁を主座とする軽度の慢性炎症であり，CRPの上昇も高感度測定キットで検出されるレベルであることから（高感度CRP），我々は両者を区別するためにmicroinflammationと呼んでいる．microinflammationの基本的病態の一つは内皮細胞障害（内皮細胞の活性化）であり，他の炎症性疾患と同様に血管壁に細胞接着分子，ケモカインの発現亢進とマクロファージの浸潤を認める．

糖尿病性腎症の成因に炎症が関与するという仮説を提示して，一連の研究でこれを検証した．1993年に古田らによって糖尿病性腎症の腎組織に炎症細胞が浸潤することが報告されたが，当科の四方らは糖尿病性腎症患者と糖尿病動物の腎組織にマクロファージの浸潤とICAM-1（intercellular adhesion molecule-1）などの接着分子の発現亢進が起こることを明らかにし，糖尿病性腎症の発症進展に炎症が関与している可能性を示した[10]．さらに我々は，ICAM-1ノックアウトマウス[11]，macrophage scavenger receptor-Aノックアウトマウス[12]では，ストレプトゾトシン誘導糖尿病において糸球体内へのマクロファージの浸潤が抑制されることによって，アルブミン尿や糸球体の細胞外基質の増加が抑制されることを示し，これらの接着分子を阻害することが，炎症の抑制と腎症の治療に有用であることを示した（図4）．hydroxymethylglutaryl-CoA reductase還元酵素阻害薬（以下スタチンと略す）はコレステロール低下作用のみならず，多面的作用により動脈硬化領域で欠かすことのできない薬剤である．スタチンの多面的作用の一つは抗炎症作用である．メバロン酸経路の下流の低分子G蛋白，nuclear factor-kappa B（以下NF-κBと略す）などの転写因子の発現が抑制され，酸化ストレスの低下が惹起されることが知られている．スタチンの抗炎症作用が腎症の発症進展を抑制するという仮説を立て，糖尿病ラットにスタチンを投与したところ，血糖やコレステロール値の変化なくアルブミン尿が低下した（げっ歯類では酵素の誘導が起こるためスタチンによる長期的なコレステロール低下作用は認められない）．当科の片岡らはスタチン投与群が腎臓におけるICAM-1の発現低下，マクロファージの浸潤抑制，DNA（deoxyribonucleic acid）の酸化マーカーである8-hydroxydeoxyguanosine（以下8-OHdGと略す）の発現を抑制し，NF-κBの活性化を抑制することを報告した[13]．その後当科において炎症を制御する可能性を持つ薬剤を用いて動物モデルで検討したところ，チアゾリジン系薬[14]，免疫抑制薬[15]などでも同様のメカニズムで腎症の発症進展を抑制することが示された．

また最近糖尿病の治療において重要な位置を占めているglucagon-like peptide-1（GLP-1）受容体アゴニストは，当科の小寺らの検討により腎症においても血糖に影響されない腎症抑制効果を有し，そのメカニズムの一つとしてマクロファージの腎組織への浸潤抑制，NF-κBの発現抑制，酸化ストレスの抑制などを含む炎症の抑制が示された[16]．GLP-1受容体は膵臓のみならずマクロファージ，腎内皮細胞にも発現しており，

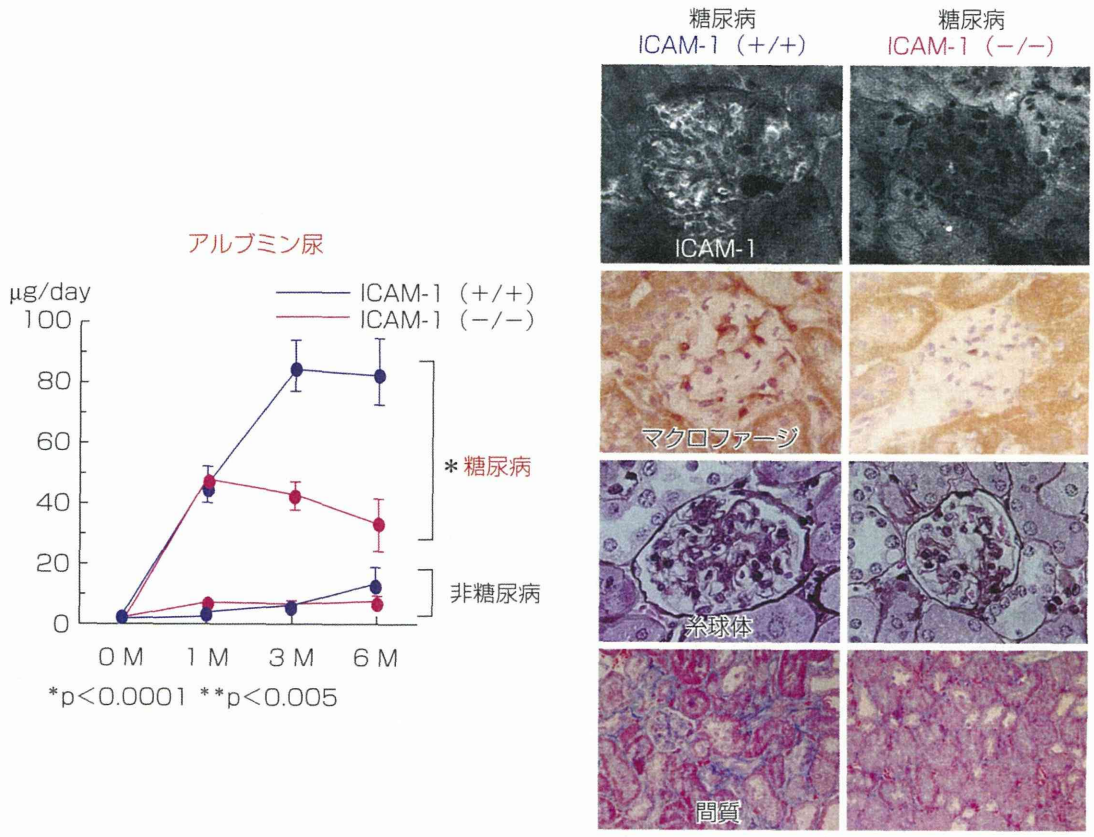

図4. ストレプトゾトシン誘発糖尿病ICAM-1ノックアウトマウスにおける糖尿病性腎症進展抑制効果

抗炎症作用にはマクロファージや内皮細胞への直接作用も関与していると考えられる．インクレチン製剤の血糖降下薬としての有用性に留まらない多面的効果についての更なる可能性と知見の集積が示唆される．さらに，当科ではインスリン抵抗性や肥満の改善に効果を期待されるperoxisome proliferator-activated receptor-δ（PPARδ）アゴニストに抗炎症作用を介した腎症抑制作用が認められると報告し[17]，今後抗炎症作用を軸とした新たな腎症治療薬についても研究が進んでいくことを期待するものである．

炎症の制御は，血糖・血圧コントロール，レニン-アンジオテンシン系の制御とともに腎症の発症進展抑制の一角を担う治療法となる可能性がある．特にDPP-4（dipeptidyl peptidase-4）阻害薬やGLP-1受容体アゴニスト，PPARファミリーのアゴニストなどの新規薬剤については，血糖コントロールを越えた血管合併症の制御の可能性も有しており，今後更なる知見の集積が待たれる．

4. 糖尿病性腎症のバイオマーカー

早期糖尿病性腎症のgold standardは微量アルブミン尿である．しかし，アルブミン尿は高血圧（良性腎硬化症），高度肥満，メタボリック・シンドロームでも陽性になるので注意が必要である．IV型コラーゲン定量が糖尿病性腎症の早期診断の指標としての意義を初めて報告した[18]．IV型コラーゲンは生体の細胞外マトリックスの構成成分であり，腎では主として糸球体基底膜に分布している．糖尿病性腎症では，糸球体の基底膜肥厚とメサンギウム領域の拡大が特徴的な変化であり，これはIV型コラーゲンを主体と

する細胞外マトリックスの増加に起因する．このため尿中アルブミンなどの血中由来蛋白が，糸球体の透過性異常を反映するのに対し，尿中IV型コラーゲンは，糸球体組織由来であるため糸球体の傷害自体を反映する指標と考えることができる．糖尿病性腎症において尿中IV型コラーゲンは，尿中アルブミン値が正常域を示す腎症前期（第一期）においても上昇し，本法は早期の診断並びに病態の進展予知に有用である．また，血清中の高感度CRPや種々の炎症関連サイトカインは糖尿病患者で上昇することが報告されてきた．活性化マクロファージから分泌されるinterleukin-18（IL-18）は冠動脈疾患患者の予後予測因子として有用であることが知られているが，当科の中村らは糖尿病患者の血清中IL-18が頸動脈の内膜中膜複合体，脈波伝播速度とともに尿中アルブミン排泄量と相関することを報告した[19]．同様に，当科の梶谷らはtumor necrosis factor（TNF-α）が尿中アルブミン排泄量や動脈硬化マーカーと相関することを示した[20]．これらは他の炎症関連サイトカインやICAM-1発現を促進させることが知られており，動脈硬化と腎症に共通する炎症メカニズムの一端を担う重要な因子と考えられる．また我々は2型糖尿病患者において尿中のprostaglandin D synthase（PGDS）排泄量が，心血管イベントの発生と関連があり，新たな心血管リスクマーカーとして報告した[21]．

5. 糖尿病性腎症の治療とエビデンスの発信

わが国から発信されたエビデンスとして最も重要なものは，アンジオテンシン変換酵素阻害薬の効果を世界に先駆けて報告した田熊らの研究である．田熊らの報告がその後のACE阻害薬やARB（angiotensin receptor blocker）のエビデンスの構築を導く先端的な研究であると考えられる．また熊本スタディーでは2型糖尿病において，厳格な血糖コントロールが腎症の一次予防，二次予防いずれにおいても効果が認められ，2型糖尿病においても腎症の発症・進展の抑制に血糖管理が重要であることを実証した研究として高く評価されている．このように質の高い研究がわが国から発信されているものの，その数は欧米と比較して極端に少ないと思われる．筆者らは514人の2型糖尿病患者を対象とした我が国最初の大規模臨床試験であるINNOVATION studyでは，telmisartanが，微量アルブミン尿を呈する日本人2型糖尿病患者において，プラセボに比し有意に顕性腎症への移行を抑制し，この効果は，治療開始時の高血圧の有無に関係なく認められた[22]．近年，強力な治療介入によりネフローゼ症候群が寛解した複数の糖尿病性腎症の症例が報告されている．これらの知見から，集約的な治療を行うことにより，顕性腎症期の症例でも寛解が可能であると期待されるが，大規模臨床試験によるエビデンスは存在しない．

さらに著者らは顕性蛋白尿を呈する2型糖尿病に伴う糖尿病性腎症患者におけるolmesartanの腎症進展抑制作用を検討した（ORIENT試験）．血清クレアチニンの2倍化，末期腎不全，死亡のいずれか最も早く出現した事象を主要評価項目とした．その結果，尿蛋白を有意に減少させたものの，腎複合エンドポイントにおいてはACE阻害薬投与下においては更なる併用効果を認めなかった．特にrapid GFR（glomerular filtration rate）declinerと考えられる比較的急速に腎機能が低下した群では併用効果がなかった．一方心血管系複合エンドポイントでは，プラセボ群と比較して36％有意に抑制した[23,24]．

我々は，2005年より厚生労働省研究事業として，Diabetic Nephropathy Remission and Regression Team Trial（DNETT-Japan）を開始した[25]．本研究は，顕性腎症（3期～4期）を伴う2型糖尿病患者を対象に，医師と糖尿病療養指導士（CDEJ）を中心としたコメディカルスタッフが参加するチーム医療によって強力な治療介入

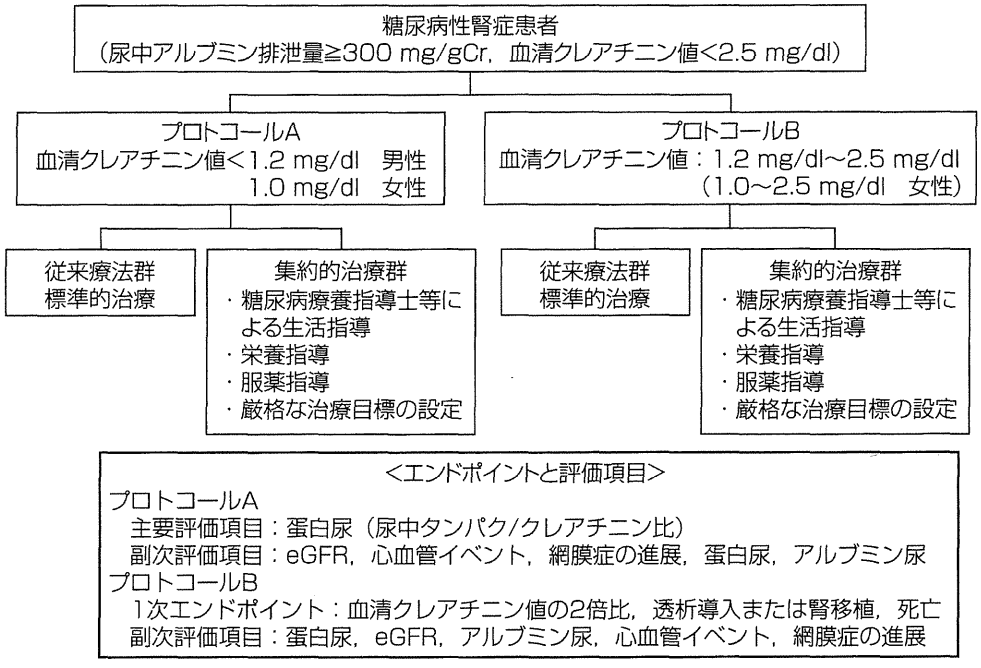

図5. DNETT-Japanの研究プロトコール

表. DNETT-Japanの治療法と目標値

	従来療法群	集約的治療群
血糖管理（JDS値）	HbA1c<6.5%	HbA1c<5.8%
血圧管理	<130/80 mmHg	<125/75 mmHg ACE阻害薬，ARBを併用 家庭血圧測定
脂質管理	LDL.cho<120 mg/dl	LDL.cho<100 mg/dl スタチン系薬剤を使用
食事：エネルギー	25～30 kcal/kg/日	30 kcal/kg/日
蛋白質	1.0 g/kg/日	0.8 g/kg/日
食塩	6 g/日	5 g/日
その他		服薬指導・禁煙指導・生活指導

を行う（集約的治療）ことにより，腎症の進展を抑制できるか否か，更には寛解させることが可能であるかを検証する多施設共同無作為化臨床試験である．対象は顕性腎症であり，プロトコールAでは腎機能が比較的保たれている群（第3期）を対象として蛋白尿の減少効果を主要評価項目としている（図5）．プロトコールBでは血清クレアチニン値の上昇が見られる症例（第4期）を対象に血清クレアチニン値の2倍化，透析療法への導入または腎移植，死亡を複合エンドポイントとして，集約的治療法における腎症の進行抑制効果を検討する（図5）．両プロトコールとも，強力な治療介入を行う集約的治療群と，従来の治療を継続する従来療法群の2群に無作為に割付けて5年間観察する．治療目標値は，従来療法群では日本糖尿病学会，日本高血圧学会，日本動脈硬化学会が提唱している治療ガイドラインに準拠しており，集約的治療法群の場合は，これよりも更に厳しい治療目標を設定した（表）．薬物療法は，従来療法群の場合は現在

の標準的な治療を継続し，集約的治療群では降圧薬としてACE阻害薬とARB，高脂血症治療薬としてHMG-CoA還元酵素阻害薬（スタチン）を，サプリメントとしてマルチビタミンを必ず使用する．食事療法は，デジタルカメラを用いた食事記録などを参考に，管理栄養士が栄養指導を行う．また，集約的治療群では，家庭血圧計による早朝血圧の測定，禁煙指導，服薬状況の厳密なチェックを行い，治療効果の向上を図る．本研究では，2006年末までに全国の約130施設のご参加を得て，310症例が観察期間に入り，200症例が登録されており，現在1回目の中間解析を行っているところである．上記のように，DNETT-Japanではチーム医療によって可能な限り積極的な治療介入を行うことにより，腎症の進展阻止・寛解が可能か否かを検証するとともに，腎症の治療法を確立することを目指している．

おわりに

糖尿病性腎症の発症・進展には種々のメカニズムが関与していることを示してきたが，それらの種々病態に介入するためには，チーム医療による集約的治療が重要であると考えている．今後も基礎研究と臨床研究を両輪として，糖尿病性腎症による腎不全や心血管病を抑制したいと考えている．

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