

How Reliable Is Estimation of Glomerular Filtration Rate at Diagnosis of Type 2 Diabetes?

RICHARD A. CHUDLEIGH, MRCP
GARETH DUNSEATH, MPHIL
WILLIAM EVANS, PHD
JOHN N. HARVEY, MD, FRCP

PHILIP EVANS, MD, FRCP
RICHARD OLLERTON, PHD
DAVID R. OWENS, MD, FRCP

OBJECTIVE — The Cockcroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD) equations previously have been recommended to estimate glomerular filtration rate (GFR). We compared both estimates with true GFR, measured by the isotopic ^{51}Cr -EDTA method, in newly diagnosed, treatment-naïve subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS — A total of 292 mainly normoalbuminuric (241 of 292) subjects were recruited. Subjects were classified as having mild renal impairment (group 1, $\text{GFR} < 90 \text{ ml/min per } 1.73 \text{ m}^2$) or normal renal function (group 2, $\text{GFR} \geq 90 \text{ ml/min per } 1.73 \text{ m}^2$). Estimated GFR (eGFR) was calculated by the CG and MDRD equations. Blood samples drawn at 44, 120, 180, and 240 min after administration of 1 MBq of ^{51}Cr -EDTA were used to measure isotopic GFR (iGFR).

RESULTS — For subjects in group 1, mean (\pm SD) iGFR was $83.8 \pm 4.3 \text{ ml/min per } 1.73 \text{ m}^2$. eGFR was 78.0 ± 16.5 or $73.7 \pm 12.0 \text{ ml/min per } 1.73 \text{ m}^2$ using CG and MDRD equations, respectively. Ninety-five percent CIs for method bias were -11.1 to -0.6 using CG and -14.4 to -7.0 using MDRD. Ninety-five percent limits of agreement (mean bias ± 2 SD) were -37.2 to 25.6 and -33.1 to 11.7 , respectively. In group 2, iGFR was $119.4 \pm 20.3 \text{ ml/min per } 1.73 \text{ m}^2$. eGFR was 104.4 ± 26.3 or $92.3 \pm 18.7 \text{ ml/min per } 1.73 \text{ m}^2$ using CG and MDRD equations, respectively. Ninety-five percent CIs for method bias were -17.4 to -12.5 using CG and -29.1 to -25.1 using MDRD. Ninety-five percent limits of agreement were -54.4 to 24.4 and -59.5 to 5.3 , respectively.

CONCLUSIONS — In newly diagnosed type 2 diabetic patients, particularly those with a $\text{GFR} \geq 90 \text{ ml/min per } 1.73 \text{ m}^2$, both CG and MDRD equations significantly underestimate iGFR. This highlights a limitation in the use of eGFR in the majority of diabetic subjects outside the setting of chronic kidney disease.

Diabetes Care 30:300–305, 2007

The prevalence of chronic kidney disease (CKD) continues to escalate at an alarming rate (1–3). In the U.K., the incidence of end-stage renal disease (ESRD) has doubled in the past 10 years and this increase is projected to continue to rise at a rate of 5–8% per annum (2). In the U.S. in 2003, there were 325,000 individuals receiving renal replacement

therapy (RRT) at a cost of \$18.1 billion per annum, 45% of these were diabetic patients (3). The number receiving RRT in the U.S. is anticipated to double by 2010 (4), clearly producing a significant economic burden. The number of patients with ESRD underestimates the entire burden of CKD. Whole-population screening surveys performed in Europe (5) and the

U.S. (6) have identified that between 6 and 11% of this population have a degree of CKD; this number increases to 50–60% when at risk groups are screened (6).

Diabetes is the leading cause of ESRD in developed countries, accounting for 18 and 36% of new cases of RRT in the U.K. and Germany, respectively, in 2001 (7) and 45% of new cases in the U.S. in 2003 (3). Differences in incidence between developed countries are likely a reflection of racial and ethnic mix. In the U.S., the incidence of ESRD is lower among Caucasian compared with African-American people (7). Racial factors also play a role in the greater susceptibility of African and Native Americans to CKD related to diabetes and hypertension (8), as well as the more rapid rate of progression of CKD seen in these groups (9). Other contributory factors related to lower disease prevalence, underreferral of patients, better management of diabetes, and higher death rates from cardiovascular disease (10) may account for the differences in incidence of ESRD seen between European countries.

There is strong evidence to show that early detection of diabetic nephropathy, resulting in timely intervention with particular attention to blood pressure control (thus limiting proteinuria), glycemic control, smoking cessation, and attenuation of cardiovascular risk, can improve long-term outcomes (11–21) and retard progression to ESRD (19,20). The clear implication of this evidence is that to achieve maximum benefit, current health care strategies must ensure detection of diabetic nephropathy as early as possible.

Although not universally accepted, the National Service Framework for Renal Services in the U.K. recommends the adoption of formula-derived estimates of GFR (eGFR) in the annual evaluation of all patients with diabetes (22). It is anticipated that this process will aid early identification and therefore improve long-term outcomes for those with diabetic nephropathy. The recently developed four-variable Modification of Diet in Renal Disease (MDRD) equation (23), which estimates GFR according to serum creati-

From the Diabetes Research Unit, Llandough Hospital, Cardiff, U.K.

Address correspondence and reprint requests to Richard A. Chudleigh, Llandough Hospital, Diabetes Research Unit, Penlan Road Penarth, Cardiff CF64 2XX. E-mail: rachudleigh@hotmail.com.

Received for publication 9 August 2006 and accepted in revised form 25 October 2006.

Abbreviations: BSA, body surface area; CG, Cockcroft-Gault; CKD, chronic kidney disease; eGFR, estimated GFR; GFR, glomerular filtration rate; ESRD, end-stage renal disease; iGFR, isotopic GFR; MDRD, Modification of Diet in Renal Disease; RRT, renal replacement therapy.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-1688

© 2007 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Table 1—Demographic data

	All subjects	Group 1 (iGFR <90)	Group 2 (iGFR ≥90)
n	292	37	255
Men/women	219/73	25/12	194/61
Age (years)	55.3 ± 9.4	62.8 ± 6.4	54.2 ± 9.3*
Weight (kg)	92.0 ± 17	88.0 ± 16.7	92.5 ± 17.0
BMI (kg/m ²)	31.5 ± 5.6	30.9 ± 6.0	31.6 ± 5.5
A1C (%)	7.79 ± 2.00	7.16 ± 1.83	7.88 ± 2.01*
Fasting plasma glucose (mmol/l)	9.70 ± 3.09	8.44 ± 2.49	9.87 ± 3.13*
Creatinine (μmol/l)	79.9 ± 14.8	90.7 ± 16.1	78.4 ± 14.0*
Systolic blood pressure (mmHg)	136 ± 20	144 ± 22	135 ± 19*
Diastolic blood pressure (mmHg)	81 ± 10	80 ± 10	82 ± 10

Data are means ± SD. **P* < 0.05 for difference between means of group 1 and group 2.

nine, age, sex, and ethnic origin, is being widely advocated (22,24).

eGFR values derived by the MDRD and the traditional Cockcroft-Gault (CG) equations have been validated in CKD (25–30); however, there is concern that they underestimate GFR in the vast majority of individuals with normal or near-normal renal function (31,32). Recent work by Parving and colleagues (33) in type 2 diabetic subjects with incipient and established nephropathy found the performance of eGFR to be unacceptable for monitoring kidney function in type 2 diabetic patients. Our study was designed to explore the relationship between the CG- and MDRD-derived eGFR and the reference ⁵¹Cr-EDTA isotopically measured GFR in newly diagnosed, treatment-naïve subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Subjects for this study were recruited from a long-term, local ethics committee-approved follow-up study of type 2 diabetic subjects performed at the University Hospital of Wales, Heath Park, Cardiff, U.K., and Llandough Hospital, Cardiff, U.K. The study population consisted of 292 newly diagnosed, treatment-naïve type 2 diabetic subjects recruited between 1996 and 2005 who had a reference isotopic ⁵¹Cr-EDTA GFR (iGFR) measurement and sufficient clinical and biochemical data for inclusion. Subjects were diagnosed according to World Health Organization criteria at the time of recruitment into the study (34,35). The vast majority of subjects were Caucasian, and no subjects were of African-American origin.

Clinical methods

At 0830 h, following an overnight fast, a urine specimen was collected, anthropo-

metric measurements taken, and blood pressure measured in the recumbent position after 10 min rest. Subjects were intravenously cannulated and blood samples drawn for blood glucose, A1C, and serum creatinine. Subsequently, a single intravenous injection containing 1 MBq ⁵¹Cr-EDTA was administered at 0 min, with further blood sampling at 44, 120, 180, and 240 min. Blood was collected into heparinized tubes and centrifuged at 4°C.

Laboratory methods

The reference iGFR was obtained by a single-injection plasma clearance method corrected for body surface area (BSA). The simplified ⁵¹Cr-EDTA clearance method used has been validated against plasma clearance determined by multiple sampling (36). The four-sample method used allowed estimation using a two-compartment model. A close correlation between total plasma clearance of ⁵¹Cr-EDTA and insulin clearance determined by the classical technique has been shown previously (37).

Serum creatinine levels were determined using the OCD (J&J) dry-slide system on the Vitros 750 × RC and 950 analyzer. The laboratory reported that the coefficient of variation of the assay was 4.2% at a creatinine concentration of 103 μmol/l and 1.92% at a creatinine concentration of 516 μmol/l. Creatinine measurement in our hospital was validated at intervals by measurement of samples from the Welsh External Quality Assurance Scheme.

Estimation of GFR

To estimate GFR, the CG formula for creatinine clearance corrected for BSA and the four-variable abbreviated MDRD formula, as recommended for use in the U.K.

CKD guidelines (24), were used. The formulas are as follows: 1) CG formula (27): eGFR (ml/min per 1.73 m²) = [140 – age (years)] × weight (kg) × k × c serum creatinine (μmol/l), where k is 1.23 for men and 1.04 for women and c adjusts for BSA (33). c = 1.73/BSA, with BSA calculated using the following DuBois (38) formula: BSA (m²) = [weight (kg)]^{0.425} × [height (cm)]^{0.725} × 0.007184; and 2) the abbreviated four-variable MDRD formula (23): eGFR (ml/min per 1.73 m²) = 186 × [serum creatinine (μmol/l)/88.4]^{–1.154} × [age (years)]^{–0.203} × (0.742 if female) × (1.210 if African American).

Statistical analysis

Data were assessed graphically for serial correlation. Subjects were grouped by iGFR, with group 1 having iGFR 60–89 ml/min per 1.73 m² and group 2 having iGFR ≥90 ml/min per 1.73 m². eGFR results derived by the CG and MDRD formulas were compared with iGFR by means of two-tailed, paired *t* tests (confirmed by nonparametric equivalents for nonnormal distributions), χ^2 test for proportions, linear regression, and the κ statistic for rater agreement. Regression goodness of fit and other statistical method assumptions were checked graphically and by use of relevant statistics as appropriate. All calculations were performed using SPSS (version 12.0.1; SPSS) and S-PLUS (version 7.0; Insightful) software packages. Results are presented as means ± SD (95% CI), unless otherwise indicated. *P* < 0.05 was taken to indicate statistical significance. Sample size calculations indicated that the study had at least 80% power to detect a mean difference in GFR of 5 ml/min per 1.73 m².

RESULTS— The demographic characteristics of the 292 study participants are summarized in Table 1. Study subjects were largely normoalbuminuric (241 of 292 [83%]). Table 1 shows that subjects in group 1 had a higher mean age than those in group 2. There was no significant difference in weight or BMI between the groups. However, consistent with a lower iGFR, mean serum creatinine concentration was greater in group 1 than group 2.

The performance of the CG and MDRD formula-derived eGFR to estimate iGFR is presented in Table 2. Performance was assessed by use of bias (mean difference between eGFR and iGFR), precision (SD of the bias), accuracy (proportion of eGFR results within 10 and 30% of

Table 2—Predictive performance of the CG and the MDRD formulae

iGFR [median (interquartile range)]	All subjects (n = 292)			Group 1 (iGFR <90; n = 37)			Group 2 (iGFR ≥90; n = 255)		
	CG	MDRD	CG	MDRD	CG	MDRD	CG	MDRD	
eGFR [median (interquartile range)]	101.1 (26.8)	89.9 (19.0)	78.0 (16.5); 76 (69–88.5)	73.7 (12.0); 73 (64–82)	104.4 (26.3); 100 (87–120)	92.3 (18.7); 89 (78–103)			
Bias	-13.8 (-16.1 to -11.6)	-25.0 (-26.9 to -23.1)	-5.8 (-11.1 to -0.6)	-10.7 (-14.4 to -7.0)	-15.0 (-17.4 to -12.5)	-27.1 (-29.1 to -25.1)			
Precision	19.5	16.6	15.7	11.2	19.7	16.2			
95% limits of agreement	(-52.8 to 25.2)	(-58.2 to 8.2)	(-37.2 to 25.6)	(-33.1 to 11.7)	(-54.4 to 24.4)	(-59.5 to 5.3)			
Accuracy 10%	29% (24–35)	15% (11–19)	32% (19–50)	27% (14–44)	29% (23–35)	13% (9–18)			
Accuracy 30%	86% (81–89)	79% (74–83)	86% (17–95)	95% (80–99)	85% (80–89)	76% (71–81)			
R ²	0.490	0.476	0.093*	0.119	0.450	0.429			
Gradient	0.59 (0.52–0.65)	0.81 (0.71–0.91)	0.08 (-0.01 to 0.17)	0.13 (0.01–0.24)	0.52 (0.45–0.59)	0.71 (0.61–0.81)			
Intercept	55.7 (48.5–63.0)	41.9 (32.9–51.0)	77.6 (70.8–84.4)	74.7 (66.1–83.3)	65.6 (57.9–73.2)	53.8 (44.2–63.3)			

Data are means ± SD (95% CI), unless otherwise indicated. All R values were positive and, with one exception*, significantly different from zero.

iGFR), and linear regression (R² values, regression equation gradient and intercept for iGFR versus eGFR).

Positive correlations were observed between eGFR and iGFR for all groups, although these were reduced for the lower iGFR group. In Table 2, the R² values indicate that there were significant proportions of iGFR variability unexplained by either formula (over 50% in all cases). Values for bias show that on average the formulas significantly underestimated iGFR, while the precision and accuracy data indicate wide prediction intervals of iGFR for a given eGFR. The wide 95% limits of agreement, which range from negative to positive values, further highlights the poor estimates provided by the CG and MDRD methods. Gradient and intercept results also highlight scale and location differences. These are further illustrated in Fig. 1.

A comparison of eGFR- and iGFR-derived U.K. CKD stages was also made, and the percentage agreements in classification are shown in Table 3. The κ values, which reflect the degree of agreement above chance between eGFR and iGFR classification, indicate poor agreement using the MDRD formula and only fair agreement when the CG formula is used (39).

CONCLUSIONS— Formula-derived eGFR results have become widely used in clinical practice. The CG and MDRD equations have been validated in patients with CKD and are currently used to stratify CKD in Europe and North America (24,40,41). However, these equations do have recognized limitations, including a tendency to significantly underestimate higher levels of GFR (26,31,33,42,43). Additionally, Parving and colleagues (33) demonstrated that in type 2 diabetic subjects with macroalbuminuria eGFR had a poor sensitivity to detect GFR values <60 ml/min per 1.73 m².

In our study of newly diagnosed, treatment-naïve type 2 diabetic subjects, statistically significant correlations between eGFR derived by the CG and four-variable MDRD formulas with iGFR measured by ⁵¹Cr-EDTA were observed. Despite this, the performance of formula-derived eGFRs to estimate measured iGFR results generally was poor in terms of bias, precision, and accuracy.

Both formulas introduced significant biases and underestimated iGFR. This was most pronounced when applying either formula to subjects with iGFR >90 ml/

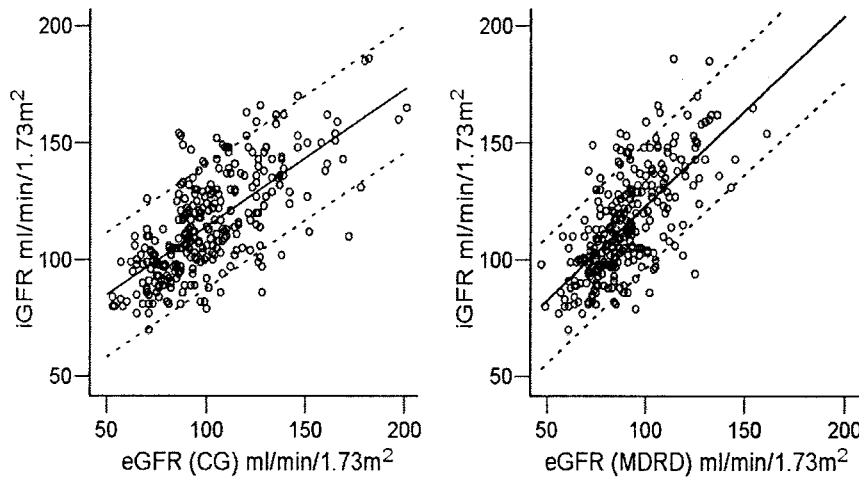


Figure 1—Relation of CG- and MDRD-calculated eGFR with ^{51}Cr -EDTA-measured iGFR. The solid line represents the regression line, and the dotted lines represent 95% prediction intervals for iGFR based on eGFR.

min per 1.73 m^2 . These findings echo and extend those of Parving and colleagues (33) who studied type 2 diabetic subjects with incipient or overt nephropathy.

Both formulas lacked precision, with wide prediction intervals for iGFR based on eGFR as illustrated in Fig. 1. Overall, the performance was particularly poor for subjects with iGFR in the range of 60–89 ml/min per 1.73 m^2 . While the difficulty in interpreting eGFR values has been demonstrated in other patient groups (33,44,45), this is the first large study to show this in newly diagnosed, treatment-naïve and mainly normoalbuminuric type 2 diabetic subjects.

The eGFR formulae were designed for application in patients with GFR <60 ml/min per 1.73 m^2 (27,28). They also have been shown to be reliable in type 2 diabetic patients with severe renal impairment (46). However, in the U.K. the National Service Framework for Renal Services now recommends the use of eGFR for renal assessment in all diabetic patients (22). This may be problematic, as

this is a different population from which the equations were derived. In our study, there was little agreement above chance between the eGFR-derived stage of CKD and that derived using iGFR, as reflected by the low κ scores.

Diabetic patients, although at higher risk of CKD than the normal population, generally have normal renal function. According to our results, use of these equations in isolation as a screening tool will lead to an overestimation of the number of diabetic patients with renal impairment. From our study, 14% of patients with GFR between 60 and 89 ml/min per 1.73 m^2 would be classed as stage 3 U.K. CKD with either formula. In isolation this would be misleading considering the low sensitivity of these tests to detect impaired renal function. Parving and colleagues (33) demonstrated only 72% sensitivity for the MDRD formula and 66% for the CG formula to detect GFR values <60 ml/min per 1.73 m^2 .

Assessment of serum creatinine clearly plays a significant role in the eGFR

formulae. There are reports (47–49) of the impact of variation in calibration of the creatinine assay having an adverse impact on the performance of eGFR to estimate GFR, particularly at low levels of serum creatinine (50). Creatinine assays can be calibrated by gas chromatography isotope dilution mass spectrometry to give a gold standard creatinine value. In the U.S., the National Kidney Education Program has initiated a standardization program to minimize this variation of creatinine measurement (50), and the program is expected to be complete by 2008. Despite being more precise and accurate, these methods give serum creatinine values, which are lower compared with the widely used modified Jaffe method (50). Use of the standardized values would then give higher GFR estimates. This has led to the MDRD equation being reexpressed in 2005 for use with a standardized serum creatinine assay (51). The authors of the updated equation recommend that the original four-variable MDRD equation should continue to be used until the standardization of creatinine assays is complete (49). During the course of our study, creatinine measurements were standardized by measurement of common samples in the Welsh External Quality Assurance Scheme but were not calibrated to the MDRD laboratory. This is a potential limitation of our study; however, until standardization is widespread our results reflect current clinical practice.

Due to the recognized deficiencies of serum creatinine to detect mild renal impairment, even when used with prediction equations (26,31,33,42,43), there is interest in cystatin C, a nonglycosylated basic protein, as a potential endogenous filtration marker of GFR. There is supportive evidence that the reciprocal of cystatin C correlates more closely with isotopic GFR than the CG or MDRD equa-

Table 3—U.K. CKD staging of subjects in groups 1 and 2

	CG eGFR κ = 0.24			MDRD eGFR κ = 0.15		
	U.K. CKD stage 3 (GFR <60)	U.K. CKD stage 2 (GFR 60–89)	U.K. CKD stage 1 (GFR ≥ 90)	U.K. CKD stage 3 (GFR <60)	U.K. CKD stage 2 (GFR 60–89)	U.K. CKD stage 1 (GFR ≥ 90)
n	6	100	186	7	156	129
Group 1 (GFR 60–89; n = 37)	5/37 (14)	24/37 (65)	8/37 (21)	5/37 (14)	29/37 (78)	3/37 (8)
Group 2 (GFR ≥ 90 ; n = 255)	1/255 (1)	76/255 (30)	178/255 (69)	2/255 (1)	127/255 (50)	126/255 (49)

Data are n (%).

tions in subjects with mild renal impairment (52). However, concerns remain regarding intrapatient variation and the effect of certain drugs and hormonal levels on cystatin C concentration (53). While it remains an interesting potential tool for clinical use, substantially more work is needed in different patient subgroups before cystatin C can be considered as an alternative to serum creatinine.

In summary, for patients with diabetes and preserved renal function we recommend that eGFR results not be considered in isolation but together with other indicators of CKD such as microalbuminuria, proteinuria, hematuria, or changes in creatinine concentration. It may be appropriate only to quantify eGFR results <60 ml/min per 1.73 m², since U.K. CKD stage 3 CKD has increased clinical significance, necessitating additional intervention. Unfortunately, even this is problematic due to the over diagnosis of CKD stage 3 by eGFR demonstrated in this study.

eGFR is being widely, but not universally, used in patients with and without CKD. The U.K. CKD guidelines advocate the four-variable MDRD equation because it is most accurate in CKD and most easily applicable in clinical practice. However, the current study highlights that while eGFR maybe useful in the assessment of CKD it does have significant limitations outside of this setting.

References

1. The Renal Association: UK Renal Registry: the eighth annual report, 2005. Available from http://www.renalreg.com/Report%202005/Cover_Frame2.htm. Accessed 8 August 2006
2. Lysaght MJ: Maintenance dialysis population dynamics: current trends and long-term implications. *J Am Soc Nephrol* 13: 37–40, 2002
3. United States Renal Data System: Annual data report, 2005. Available from http://www.usrds.org/adr_2005.htm. Accessed 8 August 2006
4. United States Renal Data System: Incidence and prevalence of ESRD. In *US Renal Data System 2003 Annual Data Report*. Bethesda, MD, National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Diseases, 2003, p. 47–60
5. Hillege HL, Janssen WM, Bak AA, Diercks GF, Grobbee DE, Crijns HJ, Van Gilst WH, De Zeeuw D, De Jong PE, the Prevent Study Group: Microalbuminuria is common, also in a non-diabetic, non-hypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. *J Intern Med* 249:519–526, 2001
6. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS: Prevalence of chronic kidney disease and decreased kidney function in the adult US population: third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 41:1–12, 2003
7. El Nahas AM, Bello AK: Chronic kidney disease: the global challenge. *Lancet* 365: 331–340, 2005
8. United States Renal Data System: Annual data report: incidence and prevalence of ESRD. *Am J Kidney Dis* 42 (Suppl. 5):S37–S173, 2003
9. Hsu CY, Lin F, Vittinghoff E, Shlipak MG: Racial differences in the progression from chronic renal insufficiency to end-stage renal disease in the United States. *J Am Soc Nephrol* 14:2902–2907, 2003
10. Feest TG, Rajamahesh J, Byrne C, Ahmad A, Ansell D, Burden R, Roderick PJ: Trends in adult renal replacement therapy in the UK: 1982–2002. *QJ Med* 98:21–28, 2005
11. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long term complications in insulin dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
12. Mulec H, Blohme G, Grande B, Bjorck S: The effect of metabolic control on rate of decline in renal function in insulin-dependent diabetes mellitus with overt diabetic nephropathy. *Nephrol Dial Transplant* 13:651–655, 1998
13. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
14. Levey AS, Greene T, Beck GJ, Caggiula AW, Kusek JW, Hunsicker LG, Klahr S: Dietary protein restriction and the progression of chronic renal disease: what have all the results of the MDRD study shown? *J Am Soc Nephrol* 10:2426–2439, 1999
15. Ritz E, Ogata H, Orth SR: Smoking: a factor promoting onset and progression of diabetic nephropathy. *Diabetes Metab* 26 (Suppl. 4):54–63, 2000
16. Bianchi S, Bigazzi R, Caiazza A, Campese VM: A controlled prospective study of the effects of atorvastatin on proteinuria and progression of kidney disease. *Am J Kidney Dis* 41:565–570, 2003
17. Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, Tuttle K, Douglas J, Hsueh W, Sowers J: Preserving renal function in adults with hypertension and diabetes: a consensus approach. *Am J Kidney Dis* 36:646–661, 2000
18. Heart Outcomes Prevention Study Investigators: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO HOPE substudy. *Lancet* 355:253–259, 2000
19. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P: The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 345: 870–878, 2001
20. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rhode R, Raz I: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345:851–860, 2001
21. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snappin SM, Zhang Z, Shahinfar S: Effects of Losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345 :861–869, 2001. Available from <http://www.kidney.org/campaigns/Renal-nsf--t2.-df>. Accessed 19 December 2006
22. Department of Health Renal Team: The National Service Framework for Renal Services. Part 2: chronic kidney disease, acute renal failure and end of life care, 2005. Available from <http://www.kidney.org.uk/campaigns/Renal-nsf/nsf-pt2.pdf>. Accessed 19 December 2006
23. Levey AS, Greene T, Kusek J, Beck G: A simplified equation to predict glomerular filtration rate from serum creatinine (Abstract). *J Am Soc Nephrol* 11:155A, 2000
24. Joint Speciality Committee on Renal Medicine of the Royal College of Physicians and the Renal Association, the Royal College of General Practitioners: *Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral*. London, Royal College of Physicians, 2006
25. Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG: Using serum creatinine to estimate glomerular filtration rate accuracy in good health and in chronic kidney disease. *Ann Intern Med* 141:929–937, 2004
26. Poggio ED, Wang X, Greene T, Van Lente F, Hall PM: Performance of the modification of diet in renal disease and Cockcroft Gault equations in the estimation of GFR in health and in chronic kidney disease. *J Am Soc Nephrol* 16:459–466, 2005
27. Cockcroft DW, Gault HM: Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31–41, 1976
28. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method of estimate glomerular filtration rate from serum creatinine: a new prediction equation: Modification of Diet in Renal

- nal Disease Study Group. *Ann Intern Med* 130:461–470, 1999
29. Lamb EJ, Webb MC, Simpson DE, Coakley AJ, Newman DJ, O'Riordan SE: Estimation of glomerular filtration rate in older patients with chronic renal insufficiency: is the Modification of Diet in Renal Disease formula an improvement? *J Am Geriatr Soc* 51:1012–1017, 2003
 30. Lewis J, Agodoa L, Cheek D, Greene T, Middleton J, O'Connor D, Ojo A, Phillips R, Sika M, Wright J Jr: Comparison of cross-sectional renal function measurements in African Americans with hypertensive nephrosclerosis and of primary formulas to estimate glomerular filtration rate. *Am J Kidney Dis* 38:744–753, 2001
 31. Vervoort G, Willems HL, Wetzels JF: Assessment of glomerular filtration rate in healthy subjects and normoalbuminuric diabetic patients: validity of a new (MDRD) prediction equation. *Nephrol Dial Transplant* 17:1909–1913, 2002
 32. Bostom AG, Kronenberg F, Ritz E: Predictive performance of renal function equations for patients with chronic kidney disease and normal serum creatinine levels. *J Am Soc Nephrol* 13:2140–2144, 2002
 33. Rossing P, Rossing K, Gaede P, Pedersen O, Parving HH: Monitoring kidney function in type 2 diabetic patients with incipient and overt diabetic nephropathy. *Diabetes Care* 29:1024–1030, 2006
 34. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group*. Geneva, World Health Org., 1985 (Tech. Rep. Ser. no., 727)
 35. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
 36. Vora JP, Burch A, Owens DR, Peters JP: Simultaneous determination of glomerular filtration rate and effective renal plasma flow. *Clin Phys Physiol Meas* 12: 269–277, 1991
 37. Brochner-Mortensen J: Current status on assessment and measurement of glomerular filtration rate. *Clin Physiol* 5:1–17, 1985
 38. DuBois D, DuBois EF: A formula to estimate the approximate surface area if height and weight are known. *Ann Internal Med* 17:863–871, 1916
 39. Medical University of South Carolina: Kapa [article online]. Available from <http://www.musc.edu/dc/crebm/kappa.html>. Accessed 8 August 2006
 40. European Best Practice Guidelines for Haemodialysis (Part 1): Section I: measurement of renal function, when to refer and when to start dialysis. *Nephrol Dial Transplant* 17 (Suppl. 7):S7–S15, 2002
 41. National Kidney Foundation: K/DOQI Clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kid Dis* 39 (Suppl. 2):S1–S266, 2002
 42. Lin J, Knight EL, Hogan ML, Singh AK: A Comparison of prediction equations for estimating glomerular filtration rate in adults without kidney disease. *J Am Soc Nephrol* 14:2573–2580, 2003
 43. Nielsen S, Rehling M, Schmitz A, Mogenssen CE: Validity of rapid estimation of glomerular filtration rate in type 2 diabetic patients with normal renal function. *Nephrol Dial Transplant* 14:615–619, 1999
 44. Hallan S, Asberg A, Lindberg M, Johnsen H: Validation of the Modification of Diet in Renal disease formula for estimating GFR with special emphasis on calibration of the serum creatinine assay. *Am J Kidney Dis* 44:84–93, 2004
 45. Froissart M, Rossert J, Jacquot C, Paillard M, Houillier P: Predictive performance of the Modification of Diet in Renal Disease and Cockcroft-Gault equations for estimating renal function. *J Am Soc Nephrol* 16: 763–773, 2005
 46. Rigalleau V, Lasseur C, Perlemoine C, Barthe N, Raffaitin C, Liu C, Chauveau P, Baillet-Blanco L, Beauvieux MC, Combe C, Gin H: Estimation of glomerular filtration rate in diabetic subjects. *Diabetes Care* 28:838–843, 2005
 47. Murthy K, Stevens LA, Stark PC, Levey AS: Variation in serum creatinine assay calibration: a practical application to glomerular filtration rate estimation. *Kidney Int* 68:1884–1887, 2005
 48. Coresh J, Astor BC, McQuillan G, Kusek J, Greene T, Van Lente F, Levey AS: Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate the glomerular filtration rate. *Am J Kidney Dis* 39:920–929, 2002
 49. Stevens LA, Coresh J, Greene T, Levey A: Assessing kidney function: measured and estimated glomerular filtration rate. *N Engl J Med* 354:2473–2483, 2006
 50. Myers GL, Miller WG, Coresh J, Fleming J, Greenberg N, Greene T, Hostetter T, Levey AS, Panteghini M, Welch M, Eckfeldt JH: National Kidney Disease Education Program Laboratory Working Group: Recommendations for improving serum creatinine measurements: a report from the Laboratory Working Group of the National Kidney Disease Education Program. *Clin Chem* 252:5–18, 2006
 51. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek J: Expressing the MDRD study equation for estimating GFR with IMDS tracable (gold standard) serum creatinine values (Abstract). *J Am Soc Nephrol* 16:69A, 2005
 52. Dharnidharka VR, Kwon C, Stevens G: Serum cystatin C is superior to serum creatinine as a marker of kidney function: meta analysis. *Am J Kidney Dis* 40:221–226, 2002
 53. Filler G, Bokenkamp A, Hofmann W, Le Bricon T, Martinez-Bru C, Grubb A: Cystatin C as a marker of GFR: history, indications and future research. *Clin Biochem* 38:1–8, 2005