

Evidence Tables
NEPH 1 Which tests should be used in the diagnosis and management of renal disease?

Reference	Study type Evidence level	Number of patients	Patient characteristics	Aim – Laboratory methods	Outcome measures	Effect size	Source of funding
GFR estimation (eGFR)							
Poggio ED, Wang X, Greene T, Van LF, 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 2005; 16(2):459-466. Ref ID: 4844	Cross-sectional study 2+	Total population N= 1,285 CKD N = 828 T2D N= 249	Inclusion criteria The Renal Function Laboratory at the Cleveland Clinic Foundation (CCF) performed approximately 9,000 measurements of GFR by 125 I-iothalamate renal clearance (iGFR) from 1982 to 2002 and maintained a database with demographic and laboratory variables. This report is limited to data on 1,285 outpatients who were 18 yr or older, with or without CKD, and who had SCr values obtained between January 1996 and December 2002. Of these, 457 were healthy kidney donors (kidney donor group) and 828 had CKD (CKD group). A total of 249 individuals had diabetic nephropathy (DM	Aim: to evaluate the performance of the four-variable MDRD and CG equations in two distinct populations: (1) outpatients with CKD, including those with diabetic nephropathy, and (2) healthy individuals Laboratory methods: GFR measurement: GFR was measured using the renal clearance of 125 I-iothalamate. Patients received a water load before the test. Twenty-five uCu of 125 I-sodium iothalamate was injected subcutaneously without epinephrine. Serum creatinine (SCr) measurement and calibration: A blood sample obtained simultaneously with the iGFR was used to measure SCr by the modified kinetic Jaffe reaction. The mean SCr levels performed by the CCF	Bias Test Correlation Accuracy	Bias In the whole CKD group (N=828), the MDRD equation was superior to the Cockcroft-Gault equation in terms of bias. The MDRD equation slightly underestimated the measured iGFR, while the Cockcroft-Gault equation significantly overestimated the GFR (-0.5 vs. 3.5 ml/min per 1.73 m ² , p < 0.001). The MDRD equation was also significantly less biased than the Cockcroft-Gault equation in the nondiabetic CKD (N=579) subgroup, the diabetic CKD (N=249) subgroup, and in people with a measured GFR < 30 ml/min per 1.73 m ² (N=546) (p < 0.001 in each group). The MDRD and Cockcroft-Gault equations were significantly more biased in people with GFR > 60 ml/min per 1.73 m ² (N=117). The MDRD equation underestimated the measured iGFR, while the Cockcroft-Gault equation significantly overestimated the GFR (-3.5 vs. 7.9 ml/min per 1.73 m ² , p < 0.001). The equations were also biased, but to a lesser extent in patients with GFR 30-60 ml/min per 1.73 m ² . In the kidney donor control group (N=459), the Cockcroft-Gault equation	National Kidney Foundation

			<p>subgroup), and 579 had other causes of CKD (non-DM subgroup).</p> <p>1,285 outpatients (18 years or older) with or without CKD who had SCr values measured between Jan., 1996 and Dec., 2002.</p> <p>Exclusion criteria Not stated</p>	<p>laboratory of 411 kidney donors between 1996 and 2002 were also compared with the mean calibrated SCr levels in corresponding age, gender, and racial subgroups from the nationally representative Third National Health and Nutrition Examination Survey (NHANES III) sample of noninstitutionalized adults.</p> <p>The NHANES III mean SCr levels were based on 15,625 measurements calibrated to the MDRD laboratory based on measurements performed by the NHANES and MDRD laboratories of 554 stored frozen patient samples during 1999</p> <p>GFR estimation: Estimated GFR (eGFR) were calculated using the following equations:</p> <p>MDRD study equation GFR $= 186 \times S_{Cr}^{-1.154}$ $\times \text{age}^{-0.203} \times 0.742$ (if female) $\times 1.212$ (if black)</p> <p>Cockcroft-Gault equation $\text{GFR} = (140 - \text{age}) \times \text{weight} / [72 \times S_{Cr} \times \text{BSA} \times 0.85$ (if female)]</p>		<p>was superior to the MDRD equation in terms of bias (1.9 vs. -9.0 ml/min per 1.73 m^2, $p < 0.001$).</p> <p>Test Correlation In the CKD population, both the MDRD (R=0.90) and Cockcroft-Gault equations (R=0.89) correlated highly with measured ^{125}I-iothalamate GFR. In the kidney donor control group, neither the MDRD equation (R=0.36) nor the Cockcroft-Gault equation (R=0.41) correlated highly with measured ^{125}I-iothalamate GFR.</p> <p>Accuracy In the whole CKD group (N=828), the MDRD equation was significantly more accurate (71% accurate within 30% of the measured iGFR) than the Cockcroft-Gault equation (60% accurate within 30% of the measured iGFR, $p < 0.001$). The MDRD equation was also significantly more accurate than the Cockcroft-Gault equation in the nondiabetic CKD (74% vs. 63%, $p < 0.001$) subgroup, the diabetic CKD (63% vs. 53%, $p < 0.05$) subgroup, and in people with a measured GFR < 30 ml/min per 1.73 m^2 (68% vs. 54%, $p < 0.001$).</p> <p>There was no statistically significant difference in accuracy between the MDRD and Cockcroft-Gault equations in people with GFR 30-60 ml/min per 1.73 m^2, GFR > 60 ml/min per 1.73 m^2, or in the kidney donor control group.</p>	
Rigalleau V, Lasseur C, Perlemoine C,	Cross-sectional	N=200	Patients with diabetes who had kidney failure	Aim: a) to investigate whether the MDRD and CG	CG, MCG and MDRD formulae compared with	*Concordance study and weight-related bias	None reported

<p>Barthe N, Raffaitin C, De La FR et al. A simplified Cockcroft-Gault formula to improve the prediction of the glomerular filtration rate in diabetic patients. Diabetes & Metabolism 2006; 32(1):56-62. Ref ID: 3874</p>	<p>study 2+</p>	<p>Single site</p>	<p>or at least one kidney damaged defined by an isotopic GFR below 90mL/(min/1.73m²) and microalbuminuria of more than 30 mg/24 hours</p> <p>Exclusion criteria: dialysis, nephrotic proteinuria (>3 g/24h) or clinical edema</p> <p>Patient population:</p> <p>Concordance group (means): 58% male, age 63 yrs, type 1 29%, weight 76.1 kg, height 166 cm, BMI 27.4, HbA_{1c} 8.6%, serum creatinine 146 µmol/L</p> <p>Validation group (means): 61% male, age 63.1 yrs, type 1 33%, weight 76.8 kg, height 166 cm, BMI 27.6, HbA_{1c} 8.6%, serum creatinine 147 µmol/L</p>	<p>estimations led to a correct stratification of renal failure in 100 diabetic patients.</p> <p>b) to simplify the CG equation and validate it in another group of 100 diabetic patients</p> <p>c) to compare the performance of the 3 equations (CG, MDRD, simplified CG) for the whole population N=200</p> <p>Stratification of renal failure in to moderate (Glomerular Filtration Rate GFR = 30-60 mL/min/1.73 m², severe (15-30) or terminal (<15) using the Cockcroft-Gault (CG)</p> <p>Concordance group (N=100) Recruited from January 2001 to January 2003</p> <p>Validation group (N=100) included after January 2003</p>	<p>isotopic GFR</p>	<p>Mean isotopic GFR in the concordance group was 57.3 ± 37.5 mL/min/1.73 m². Both the CG and MDRD were well correlated with GFR (r=0.81; and r=0.83, respectively, p<0.0001 for both).</p> <p>However, CG overestimated GFR (62.2 ± 38.1; p<0.05 vs isotopic) and MDRD underestimated it (51.2 ± 4.2; p<0.01 vs isotopic). More patients were well classified according to the MDRD (p<0.01). Only 50% of the patients were well classified by both formulae (both wrong: 16% of the patients, discordant: 34%)</p> <p>Isotopic GFR and the MDRD estimation were not correlated with BMI. The CG was statistically correlated with BMI (r=0.32; p<0.005). In the 30 patients with normal bodyweight, the CG underestimated GFR (-12%; p<0.05), the MDRD did not (-4%; NS). In the 23 obese patients, the CG overestimated GFR (+ 33%; p<0.005) but the MDRD did not.</p> <p>*Concordance group and correction of the CG formula Improving the CG formula by replacing the real body weight of patients with their ideal body weight led to a marked underestimation. Body weight in the CG was replaced by its mean value (76 kg) to calculate a new formula, MCG.</p> <p>Mean MCG (60.6 ± 31.2, NS vs isotopic) was well correlated with isotopic GFR (r=0.86, p< 0.0001), and not correlated with BMI (NS). The MCG did not differ significantly from isotopic GFR in patients with normal body</p>
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						<p>weight (NS) nor in the obese patients (NS).</p> <p>*Validation of the MCG formula Mean isotopic GFR was 55.6 ± 32.2 mL/min/1.73 m². The MCG was well correlated with the isotopic GFR (mean MCG: 59.3 ± 28.6, NS vs isotopic, $r=0.79$, $p<0.0001$) and not correlated with BMI (NS), unlike the CG ($r=0.31$, $p<0.005$). In the 37 patients with a normal BMI, the MCG did not differ from the isotopic GFR (NS) in comparison the CG underestimated GFR (CG: 50.9 ± 33.8, -14%; $p<0.05$ vs isotopic). In the 30 obese patients, the MCG did not differ from the isotopic GFR (NS), whereas the CG overestimated GFR (CG: 75.0 ± 40.0, + 31%; $p<0.001$ vs isotopic).</p> <p>*Whole population Over the whole population the mean isotopic GFR was 56.5 ± 34.9 mL/min/1.73 m², the mean CG 61.2 ± 35.6 ($p<0.01$ vs isotopic) mean MCG. 60.0 ± 29.9 ($p<0.05$ vs isotopic) and the mean MDRD, 51.0 ± 24.3 ($p<0.001$ vs isotopic). The MCG was better correlated with isotopic GFR than was the CG (CG: $r=0.75$, MCG: $r=0.83$; $p<0.05$ vs CG, MDRD: $r=0.82$; $p=0.068$ vs CG).</p> <p>The ROC curves showed that the MDRD and the MCG had a better maximal accuracy for the diagnosis of moderate (N=119; Area Under Curve 0.866 for CG, 0.920 for MDRD, 0.921 for MCG; both 0.891 vs CG) and severe (N=52; AUC: 0.891 for CG, 0.930 for MDRD, 0.942 for MCG; both $p<0.05$ vs</p>
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						<p>CG) renal failure.</p> <p>The median difference between the predicted and measured GFR were -1.2 mL/min/1.73 m² for the MDRD, +4.5 for the CG and +4.6 for the MCG.</p> <p>The Bland & Altman procedure revealed a bias for the MDRD and MCG: the differences between the predicted and the measured GFR were correlated with their means (MDRD: r=0.054, p<0.0001; MCG: r=0.27, p<0.001). There was no such bias for CG.</p> <p>When the means ± SD estimations by the three formulae are categorised by deciles: under 50 mL/min/1.73 m², all of the formulae overestimated GFR, where as the MDRD underestimated higher GFR.</p> <p>*Stratification of CKD on the whole population As the MCG was more accurate for high GFR, and the MDRD was more accurate for low GFR, the MCG was used at low serum creatine values and the MDRD at high values. The best cut off for correct stratification was at 120 µmol/l creatine (147/200 well stratified).</p>	
Albuminuria – Qualitative methods (dipsticks)							
Cortes SL, Martinez RH, Hernandez JL, Rojas CE, Canales MJ, Cueto MA. Utility of the Dipstick Micraltest II in the screening of microalbuminuria of diabetes mellitus type 2 and essential hypertension. Revista	Cross-sectional study 2+	Total population N=255, T2D N=166 N=71 (29%) T2D without hypertension N=95 (39%)	Inclusion: T2D with or without hypertension, those with essential hypertension without DM Exclusion: cardiac failure, renal tract disease, acute febrile illness, UTI, haematuria,	Aim: to evaluate the utility of Micral-Test II as a screening test for microalbuminuria compares with nephelometry (timed-urine collection) in patients with T2D and non-diabetic patients with hypertension	Sensitivity Specificity PPP NPV	*Micral test II validity in those with T2D: Sensitivity 83%, Specificity 96%, Positive predictive value (PP) 95%, Negative predictive value (NP) 88%, Prevalence 42%, Exactitude 90% * The correlation between nephelometry and Micral Test II results was 0.81 (p<	Mexican Public institution

<p>de Investigacion Clinica 2006; 58(3):190-197. Ref ID: 152</p>		<p>T2D with hypertension</p> <p>Those attending 3 primary healthcare units in Mexico</p>	<p>abnormal sediment, any level of proteinuria in urinalysis, serum creatinine >2mg/dl</p>	<p>24hr urine sample tested with:</p> <p>Micral test II dipstick</p> <p>Nephelometry (gold standard)</p> <p>(microalbuminuria was defined as 20-200mg/l)</p>		<p>0.0001)</p> <p>*Duration of diabetes</p> <p>Sensitivity and PP value seemed to improve with longer duration of diabetes (sensitivity ≤5yrs 68%, 6-10yrs 87%, >10yrs 87%) (PP value ≤5yrs 91%, 6-10yrs 91%, >10yrs 97%)</p> <p>Specificity and exactitude were roughly the same throughout</p> <p>The ROC curve for the Micral test II as a diagnostic test for microalbuminuria was analysed, the calculated mean area under the ROC curve (±SEM) was 0.91±0.03 (CI 95% 0.85 to 0.96) and the corresponding best cut-off value was 30.5mg/l</p>	
<p>Incerti J. Evaluation of test for microalbuminuria screening in patients with diabetes. Nephrology Dialysis Transplantation (2005) 20: 2402 – 2407 Ref ID: 4812</p>	<p>Cross-sectional study</p> <p>Diagnostic test¹ 2+</p>	<p>N= 278</p>	<p>Inclusion criteria: Consecutive diabetic patients (n= 531) attending the Diabetes and Internal Medicine outpatient clinics at Hospital de Clinicas de Porto Alegre were prospectively recruited by one of the investigators</p> <p>Exclusion criteria: Patients with proteinuria (positive Combur-Test in a random urine sample or proteinuria >500 mg/24 h), urinary infection (positive urine culture), clinical conditions causing</p>	<p>Aim: to assess the accuracy of Urinary Albumin Concentration (UAC), urinary albumin-to-creatinine ratio (ACR), and the Micral-Test II in a random urine specimen (RUS) for microalbuminuria screening in diabetes mellitus.</p>	<p>Follow-up: N/A</p> <p><u>Urine samples and measurements</u></p> <p>Initially, 531 patients collected 531 24 h timed urine samples followed by 531 RUS collections. Both samples were excluded from the analysis if the RUS was not sterile (n=56), if it was positive for total protein (Combur-Test positive) (n=50), if more than five erythrocytes were observed per high-power field in the urinary sediment (n=0), if sediment analyses were</p>	<p>Correlations coefficients</p> <p>The correlation coefficient (278 urine samples) was:</p> <p><u>UAER vs UAC</u> 0.76 p< 0.0001</p> <p><u>UAER vs ACR</u> 0.74 p<0.0001</p> <p><u>ACR vs UAC</u> 0.86 p<0.0001</p> <p>Age and 24 h creatinuria presented a negative correlation (278 patients; r= - 0.19; p=0.002).</p> <p>No correlation was observed between age and UAER (r=0.02; p=0.74), age and UAC (r=0.07; p=0.22) and age and UACR</p>	<p>Brazilian Public institution</p>

¹ This is a study of diagnostic accuracy to evaluate three screening tests for microalbuminuria in a RUS. Measurements of timed 24 h urinary albumin excretion rate (UAER) were used as the reference standard.

		<p>dehydration (due to possibility of false positive results on albumin measurements) or any wasting diseases that could cause severe undernourishment were excluded. 278 patients were included in the final sample.</p> <p>Patient characteristics: Their main clinical features were as follows: 28 type 1 and 250 type 2 diabetic patients; 116 (41.7%) males; 57.3±13.4 years of age (16–84 years); diabetes duration of 11.6±7.7 years (1–45 years); BMI of 28.0±11.1 kg/m²; blood pressure levels of 139.8±23.5/81.8±11.9 mmHg, and serum creatinine of 0.89±0.26 mg/dl (0.5–2.0).</p>		<p>not performed (n=66), if creatinine measurements were not performed (n=28) or if the 24 h urine collection was considered to be incomplete (creatinine values <700mg for women and <1000 mg for men; n=53). Thus, 278 24 h and RUS samples were analyzed.</p> <p>The samples were classified as normoalbuminuric (UAER<20 mg/min) or microalbuminuric (UAER¼20–199 mg/min) according to UAER.</p> <p>In addition, from the 278 RUS, 130 fresh urine samples were randomly selected and used for Micral-Test II strip readings, performed at room temperature by three investigators blinded to the albumin content of the samples and to the patient's renal status.</p> <p>The cost (US currency) of microalbuminuria diagnosis per patient was calculated for UAC, UACR and the Micral- Test II, based on the cost of each test and</p>	<p>(r=0.11; p=0.08).</p> <p>To evaluate the possible effect of ageing on 24 h creatinine, UAER, UAC and UACR, patients were divided according to age tertiles. The 24 h creatinuria was lower in the highest tertile (age ≥ 65 years) in relation to the first tertile (age < 54 years) (1137.6 ± 313.7 vs 1294.9 ±414.0 mg/24 h; ANOVA, p=0.037; Bonferroni test for multiple comparisons, p= 0.028).</p> <p>Performance of UAC, UACR and Micral-Test II in a RUS for the diagnosis of microalbuminuria</p> <p>The specificity of UAC and UACR was similar when considering the 100% sensitivity cut-off points. The sensitivity and specificity of the Micral-Test II strip for a 20 mg/l cut-off point (as indicated by manufacturer) on fresh urine samples based on ROC curve analysis (N=130) were 90 and 46%, respectively.</p> <p>The comparison among the areas under the ROC curves for UAC, UACR and the Micral-Test II took into account the individual results, for each single patient (N=130), of the three screening methods being tested and of the reference test method (UAER). We observed a similar area under the UAC (0.934 ±0.032) and UACR (0.920 ±0.035) curves (p= 0.626). The area under the curve was smaller for the Micral-Test II (0.846 ±0.047) than for UAC (p=0.014)</p> <p>Cost of microalbuminuria diagnosis</p>
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					the cost of diagnostic confirmation (UAER measurement).	<p>The cost of microalbuminuria diagnosis based on the cost of each test was calculated taking into account the average time required to perform each test (albumin, 2.7 min; creatinine, 1.5 min; Micral-Test II, 1.1 min), the hourly rate of a technician (U\$3.02) and the cost of the materials used (immunoturbidometry for albumin, U\$1.07; creatinine assay, U\$0.16; Micral-Test II, U\$3.23 per strip). Considering these variables, the cost per test was U\$1.20 for UAC, U\$1.43 for UACR and U\$3.29 for Micral-Test II.</p> <p>The cost of diagnostic confirmation (UAER measurements) was calculated based on the sensitivity (100% for UAC and UACR and 90% for the Micral-Test II) and specificity (77.2% for UAC, 73.0% for UACR and 46.0% for the Micral-Test II) of the cut-off points of each test as determined by ROC curves and on a prevalence of 25% for microalbuminuria. The final cost per patient for the diagnosis of microalbuminuria was U\$1.74 for UAC, U\$2.00 for UACR (U\$1.98 for men and U\$1.93 for women), and U\$4.09 for the Micral-Test II.</p>	
Parikh CR, Fischer MJ, Estacio R, Schrier RW. Rapid microalbuminuria screening in type 2 diabetes mellitus: simplified approach	Prospective study using participants from ABCD study	N=444 urine samples from N=326 participants ²	As for the ABCD study, subjects in the ABCD were instructed to avoid strenuous exercise on the day of the urine collection ³	Aim: to evaluate Micral test strips (qualitative) in conjunction with a urine specific gravity determination (quantitative) as a rapid and accurate method for detecting	Microalbuminuria detection was compared between Micral test strips, based on the total amount of urinary albumin found by the timed urine collections using	<p>*Micral test strips performance: Sensitivity 88%, Specificity 80%, Positive predictive value 69%, Negative predictive value 92%⁵</p> <p>*Performance by different concentration</p>	NIH/NIDDK

² N=50 samples were excluded from the initial N=494 samples for the following reasons;

³ A significant percentage of study subjects had hypertension (50%) most had fairly well preserved renal function (creatinine ≥ 1.3 mg/dl)

<p>with Micral test strips and specific gravity. [erratum appears in Nephrol Dial Transplant. 2004 Sep;19(9):2425]. Nephrology Dialysis Transplantation 2004; 19(7):1881-1885. Ref ID: 4805</p>	<p>(Appropriate Blood Pressure Control in Diabetes) 2+</p>			<p>microalbuminuria in T2D patients.</p> <p>Urine samples were collected over a 1-year period</p> <p>Urinary albumin concentration by immunoturbidimetric (gold standard)</p> <p>Urinary creatinine concentration by modified Jaffe's method</p> <p>24 and 12hr urine collections were evaluated using:</p> <p>Routine urinalysis including specific gravity by regular urine dipstick</p> <p>Urinary albumin concentration by Chemtrip Micral test strips</p>	<p>immunoturbidometry (gold standard)⁴</p>	<p>readings</p> <p>Micral test strips performed reasonably well at 0, 50 and 100mg/l with high percentage of true negatives (93%, 0mg/l), true positives (81%, 50mg/l and 91%, 100mg/l), low percentages of false negatives (7%, 0mg/l) and false positives (19%, 50mg/l and 9%, 100mg/l). At 20mg/l Micral strips did not perform well (51% false positive)</p> <p>*Specific gravity The majority, 76% of readings were at 0mg/l and 20mg/l. it appears that the imperfect performance at these levels is related (in part) to the specific gravity.</p> <p>False negatives at 0mg/l decreased as specific gravity increased (7% at ≤ 1.010, 2% at ≤ 1.025).</p> <p>For 20mg/l false positives were 83% with specific gravity of ≥ 1.025 and decreased to 42% for ≤ 1.010.</p> <p>At 50mg/l false positives increased with concentration and were 65% at specific gravity ≥ 1.025</p>	
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⁴ Albumin excretion was classified; positive – meeting/exceeding the criteria for microalbuminuria (albumin >30mg/day), negative – failing to meet the criteria for microalbuminuria (albumin <30mg/day)

⁵ Test results were unchanged when only times urine samples (excluding spot urine samples) were compared with the gold standard

Albuminuria - Quantitative methods

<p>Banerjee S, Ghosh US, Saha SJ. Role of GFR estimation in assessment of the status of nephropathy in type 2 diabetes mellitus. Journal of the Association of Physicians of India 2005; 53:181-4, 2005 Mar.:181-184. Ref ID: 4801</p>	<p>Cross-sectional study 2+</p>	<p>N= 100</p>	<p>Inclusion criteria: Consecutive patients with diagnosis of T2D were collected, screened, matched and investigated from the Diabetes Clinic of N.R.S. Medical College, Kolkata from January 2001 to December 2002.</p> <p>They were divided into 3 subgroups depending on the duration of initial detection of T2DM.</p> <p><u>Group A</u> constituted patients with < 5 years duration, <u>group B</u> 5-15 years and <u>group C</u> > 15 years duration.</p> <p>Thorough clinical examination was performed. Groups were matched⁶ by BMI, sex ratio, SBP and DBP (when the patient first presented to the research group), TC level, triglyceride level, HbA1c% and smoking status (however, they were not matched by cumulative mean plasma glucose and blood pressure, HDL</p>	<p>Aim: to analyse the status of eGFR vis-à-vis other noninvasive modes of assessment of renal involvement in T2D and assess the temporal profile of the prevalence of nephropathy with a cross sectional cohort.</p> <p>Twenty four hour urinary albumin excretion rate (UAER), estimated by immunoturbidimetric method, and serum creatinine levels (autoanalyser) were assessed on 3 occasions 0 to 4 months apart under similar clinical conditions without any water loading or diuretic therapy and the average was taken.</p> <p>Ultrasonography (USG) for renal size (contracted, normal, enlarged) and noninvasive morphology (corticomedullary differentiation present or lost) was done twice at 1-2 months interval</p> <p>DTPA renal scan for estimation of total (sum of both kidneys) glomerular filtration rate (GFR) was</p>	<p>eGFR vs UAER vs serum creatinine vs USG⁷</p>	<p>Total population =100 patients Group A (T2D dx < 5 years) N= 31 Group B (T2D dx 5-15 years) N= 40 Group C (T2D >15 years) N= 29</p> <p>UAER gr/24h Group A 0.0842 ± 0.083 Group B 0.906 ± 0.84 Group C 1.346 ± 1.28</p> <p>GFR ml/min Group A 132.57 ± 19.3 Group B 76.33 ± 20.8 Group C 40.08 ± 17.1</p> <p>Serum Creatinine Group A 0.965 ± 0.24 Group B 1.06 ± 0.16 Group C 2.52 ± 2.06</p> <p>USG (%)</p> <table border="1"> <thead> <tr> <th></th> <th>N</th> <th>LND</th> <th>LLD</th> </tr> </thead> <tbody> <tr> <td>Group A</td> <td>16%</td> <td>84%</td> <td>-</td> </tr> <tr> <td>Group B</td> <td>-</td> <td>80%</td> <td>20%</td> </tr> <tr> <td>Group C</td> <td>-</td> <td>24%</td> <td>76%</td> </tr> </tbody> </table> <p>N – normal LND – large kidney with normal corticomedullary differentiation LLD – large kidney with lost corticomedullary differentiation</p> <p>Normoalbuminuria and microalbuminuria were significantly higher in group A (25.8% and 74.2%). Macroalbuminuria was higher in both group B and C (80% and 69%).</p>		N	LND	LLD	Group A	16%	84%	-	Group B	-	80%	20%	Group C	-	24%	76%	<p>None reported</p>
	N	LND	LLD																				
Group A	16%	84%	-																				
Group B	-	80%	20%																				
Group C	-	24%	76%																				

⁶ A total of 252 patients were screened, of which 113 were excluded for the purpose of matching. 39 patients could not complete all the investigations and or was lost in follow-up.

⁷ Prior to the investigations (UAER, serum creatinine, USG, DTPA) all patients were made normoglycaemic and normotensive for at least 2 weeks

			<p>and LDL levels)</p> <p>Exclusion criteria: Patients with nonsterile urine, presence of heavy hematuria, ketone bodies, rapid deterioration of renal function and or acute nephritic syndrome, active inflammation or infection elsewhere, pregnancy, congestive cardiac failure and recently detected T2D with nephrotic range proteinuria were excluded.</p>	<p>performed once in each patient</p> <p>UAER of < 30mg/24 hr was taken to be normoalbuminuria, between 30 and 299 it was microalbuminuria and > 300 mg/24 hr was considered clinical proteinuria or macroalbuminuria.</p> <p>A GFR of < 30 ml/min was considered very low, between 30 and 110 was levelled as low, normal was between 110 and 120 and above 120 ml/min. was defined as hyperfiltration. A fasting serum creatinine value of > 1.4 mg/dl was considered to be raised creatinine</p>		<p>Most of the patients of group A and B had a large kidney with preserved corticomedullary (CM) differentiation (83.9% and 80%); only group C had a significantly higher prevalence of large kidney with loss of CM differentiation (75.9%).</p> <p>Group A showed a significantly higher prevalence of normal and raised GFR (25.8 % and 61.3%). Group B had a significantly higher prevalence of low GFR, while prevalence of very low GFR was highest in group C (37.9%).</p> <p>High level of serum creatinine was only significantly associated with group C (44.8%).</p> <p>For UAER group A had a significantly lower level compared to both B and C (p <0.01), however, there was no significant difference between group B and C with respect to the amount of both micro and macro albuminuria.</p> <p>The GFR had a progressively significant decrement from group A through Group B to C (p <0.01).</p> <p>There was no difference between group A and B as far as the serum creatinine was concerned, however, there was significant difference (p<0.01) with group C.</p> <p>Patients with raised creatinine and loss of CM differentiation on USG showed the lowest GFR, but the difference (29.8 ± 18.5 vs. 38.9 ± 14.6) was not statistically significant. Only one patient of group C</p>	
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<p>Baskar V, Venugopal H, Holland MR, Singh BM. Clinical utility of estimated glomerular filtration rates in predicting renal risk in a district diabetes population. Diabetic Medicine 2006; 23(10):1057-1060. Ref ID: 2633</p>	<p>Cross-sectional study 2+</p>	<p>N= 4,303</p>	<p>Inclusion criteria: The cross-sectional evaluation was carried out in the 4,548 patients who attended the Wolverhampton district diabetes register centre (UK) and who had routine microalbuminuria screening over the 18-month period between January 2002 and June 2003. Of these individuals, estimated GFR (eGFR) results were unavailable in 245 because of unavailability of ethnicity data and they were excluded from further analysis. There were no other exclusions</p> <p>Patient characteristics: The mean age of the cohort (N= 4,303) was 60 ± 14 years; 56% were males; 78% had Type 2 diabetes; 68% were White people, 9% were Afro-Caribbean and 23% Indo-Asian</p> <p>Median serum creatinine was 94 (range 54–993) µmol/l, urine ACR was 1.75 (0.1–875.0) mg/mmol and eGFR was 68 ± 17</p>	<p>Aim: to determine the utility of eGFR (by using the MDRD equation) in predicting renal risk over and above currently available strategies that incorporate serum creatinine and microalbuminuria in a diabetes population</p> <p>Laboratory methods: Microalbuminuria testing was done using single-spot morning urine for albumin:creatinine ratio (ACR) and those with levels > 3.5 mg/mmol were classed as having abnormal albuminuria in accordance with the recommendations of the American Diabetes Association.</p>	<p>The subjects were ranked based on their eGFR (> 90, 90–60, 60–30 and < 30 ml/min per 1.73 m²) in accordance with the staging system for chronic kidney disease recommended by the National Kidney Foundation.</p>	<p>had a GFR < 10 ml/min. Total population N= 4,303</p> <p>eGFR > 90 ml/min per 1.73 m² N= 373 (9%),</p> <p>eGFR 90-60 ml/min per 1.73 m² N= 2,634 (61%)</p> <p>eGFR 60-30 ml/min per 1.73 m² N= 1,197 (28%)</p> <p>eGFR <30 ml/min per 1.73 m² N= 99 (2%)</p> <p>Overall,, the mean age, diabetes duration and the proportion of females all rose progressively as the eGFR fell.</p> <p>The SBP, the proportion of those with hypertension (defined as SBP > 140 mmHg or the use of antihypertensive therapy) and those on antihypertensive therapy also rose significantly with falling eGFR, as did serum creatinine and urine ACR.</p> <p>The proportion of individuals with abnormal serum creatinine rose with progressive fall in eGFR (0%, 1%, 37% and 100% with creatinine > 120µ mol/l in eGFR > 90, 90–60, 60–30 and < 30 ml/min per 1.73 m², respectively), as did the proportion with abnormal albuminuria (33%, 27%, 42% and 77% with ACR > 3.5 mg/mmol).</p> <p>Diagnostic performance of albuminuria, creatinine >120 µmol to detect an eGFR< 60 ml/min/1.73 m²</p> <p>Of the 1296 individuals with an eGFR</p>	<p>South Staffordshire Medical Foundation</p>
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			(4.5–139.4) ml/min per 1.73 m ²		<p><60, 539 (42%) had abnormal serum creatinine, 579 (45%) had abnormal albuminuria and 798 (62%) had either abnormal serum creatinine or urine ACR.</p> <p>Thus a creatinine- and ACR-based strategy would have missed the renal risk of 498 (38%) individuals since they had normal values of both despite having a significantly impaired eGFR < 60 ml/min per 1.73 m²</p> <p>The proportion missed by current markers was more marked in women (N= 757) where the prevalence of those with abnormal serum creatinine, urine ACR and either were 20%, 38% and 47%, respectively, compared with 72%, 54% and 83% observed in men (N=539).</p> <p>There was no difference in performance when analysed by the type of diabetes [45%,48% and 62%, respectively, with abnormal creatinine, ACR and either in Type 1 diabetes group (N= = 223) and 41%, 44% and 62%, respectively, in Type 2 diabetes group (N== 1073)].</p> <p>When analysed by ethnic origin, White people appeared to benefit the most from eGFR, with a greater prevalence of normocreatinaemic and normoalbuminuric renal insufficiency, whereas the majority of the Afro-Caribbean group with low eGFR had either an abnormal creatinine or ACR [39%, 42% and 59%, respectively, with abnormal creatinine, ACR and either in White people (N= 997); 62%, 69% and 80%, respectively, in Afro-Caribbeans (N= 84); and 44%, 54% and 69%, respectively, in Indo-Asians (N= 210)]</p>
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<p>Maclsaac RJ, Tsalamandris C, Panagiotopoulos S, Smith TJ, McNeil KJ, Jerums G. Nonalbuminuric renal insufficiency in type 2 diabetes. <i>Diabetes Care</i> 2004; 27(1):195-200. Ref ID: 1085</p>	<p>Cross-sectional study</p> <p>2+</p>	<p>N= 301</p>	<p>Inclusion criteria: patients attending the diabetes clinic at Austin Health, a tertiary referral centre and teaching hospital of the University of Melbourne, Victoria (OZ) were studied between 1990 and 2001. Isotopic estimations of GFR were routinely performed regardless of a patient's albuminuric status.</p> <p>Exclusion criteria: patients with T1D or secondary diabetes were excluded (N= 168). Patients with T2D who had recurrent urinary tract infections or hematuria (N=9), known nondiabetic renal disease (N= 15), severe intercurrent illness such as malignancy (N= 10), symptomatic cardiac failure (N= 2), no isotopic estimation of GFR, or only one estimation of AER (N= 120) were also excluded from this analysis. The remaining 301 patients were then classified according to their GFR and AER status</p>	<p>Aim: to determine the prevalence and characteristics of patients with T2D who have impaired renal function defined as a GFR <60 ml/min 1.73m², and normoalbuminuria</p> <p>Laboratory methods: AER was measured using fresh 24-h urine collections. (on completion of each collection, a midstream specimen of urine was examined by microscopy and culture to exclude UTI and hematuria.</p> <p>GFR was measured by the plasma disappearance of isotopic DTPA.</p>	<p>Patients were divided on the basis of their:</p> <p>GFR estimation (i.e., < or ≥ 60 ml/min 1.73 m²)</p> <p>Albuminuria status (i.e., normo < 20ug/min , micro 20-200 ug/min, macro >200 ug/min⁸)</p> <p>The overall prevalence and clinical characteristics of patients with a GFR <60 ml/min 1.73m² and normoalbuminuria was compared with those who had micro or macroalbuminuria. The prevalence of normoalbuminuria associated with a GFR < or ≥ 60ml/min 1.73m² was also determined.</p> <p>In patient with a GFR <60ml/min 1.73m² and normoalbuminuria, the results of all previous AER measurements were then reviewed to identify any patients whose normoalbuminuric status was possibly related to RAS inhibitor use before the start of the study. After exclusion of these patients, and adjusted prevalence of a GFR < or ≥ 60ml/min 1.73m² and</p>	<p>Total population N= 301</p> <p>GFR status There was a significant correlation between a decreasing GFR with increasing levels of AER (r= -0.29, P<0.0001).</p> <p>A total of 192 of 301 (64%) patients had a GFR ≥ 60ml/min 1.73m² while 109 of 301 (36%) had a GFR < 60ml/min 1.73m².</p> <p>For the 109 patients with a GFR < 60l/min 1.73m² the prevalence of normo-, micro-, and macroalbuminuria in a cross-sectional survey was 43 (39%), 38 (35%), and 28 (26%), respectively.</p> <p>For the 192 patients with a GFR ≥ 60ml/min 1.73m² the prevalence of normo-, micro-, and macroalbuminuria was 115 (60%), 64 (33%), and 13 (7%), respectively.</p> <p>AER status When the 301 patients were stratified according to their AER status regardless of their GFR, 158 (52%) had normo-, 102 (34%) had micro-, and 41 (14%) had macroalbuminuria. For the 158 normoalbuminuric patients, 43 (27%) had a corresponding GFR < 60ml/min 1.73m² and 115 (73%) had a GFR ≥ 60ml/min 1.73m²</p> <p>Normoalbuminuric patients were significantly older (p<0.01) and more commonly female (p<0.01) in comparison to those with macroalbuminuria. There were no differences in the duration of</p>	<p>None reported</p>
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⁸ As determined by the geometric mean of at least two measurement collected within the same 12-month period as the GFR estimation

					normoalbuminuria was calculated.	<p>diabetes, BMI, prevalence of retinopathy, history of CVD, smoking history, HbA1c levels, SBP, DPB, TC, LDL, HDL and Tg levels among patients with a GFR <60 ml/min 1.73m2 associated with normo-, micro-, or macroalbuminuria.</p> <p>Overall there were no significant differences in the use of any antihypertensive agent specifically RAS inhibitors for patients with a GFR <60ml/min 1.73m2 and normo-, micro-, or macroalbuminuria.</p> <p>CKD & Normoalbuminuria The prevalence of a GFR <60ml/min 1.73m2 and normoalbuminuria was then calculated after excluding 23 of 43 patients whose normoalbuminuric status was possibly altered by the use of a RAS inhibitors. After this adjustment the prevalence of a <60ml/min 1.73m2 and normoalbuminuria was 20 of 86 (23%)</p>	
<p>Middleton RJ, Foley RN, Hegarty J, Cheung CM, McElduff P, Gibson JM et al. The unrecognized prevalence of chronic kidney disease in diabetes.[see comment]. Nephrology Dialysis Transplantation 2006; 21(1):88-92. Ref ID: 360</p>	<p>Cross-sectional Study 2+</p>	<p>N= 7,596 from the diabetes Electronic Patient Record - Salford (UK)</p>	<p>Inclusion criteria: All adults known to have diabetes in primary and secondary care in Salford, UK, alive with independent renal function on 1 January 2004 were included in this observational study (N= 7596).Demographic and laboratory parameters were obtained from the Electronic Patient Record.</p> <p>eGFR was determined</p>	<p>Aim: To examine the ability of serum creatinine and albuminuria to detect clinically meaningful CKD compared with estimated glomerular filtration rate (eGFR).</p>	<p>- Prevalence of CKD</p> <p>- Diagnostic performance of albuminuria, creatinine vs eGFR</p>	<p>Total population N= 7,596</p> <p>Prevalence of CKD (K/DOQI) 27.5% (N= 1,715) of the population had an eGFR <60 ml/min/1.73 m2 (stage 3-5 CKD); Of these 19.4% (N= 333) had normoalbuminuria; 20.4% (N= 350) had albuminuria, the remainder not having had albuminuria determined.</p> <p>Serum creatinine was normal (≤ 120 mmol/l) in 54.7% (N= 938) of those with eGFR <60 ml/min/1.73m2 i.e. moderate to severe CKD and ≤ 150 mmol/l in 82.2% (N= 1,409). The prevalence of eGFR <60 ml/min/1.73m2 was 16% in people <70 years old and 49% if ≥ 70</p>	None reported

⁹ Albuminuria= all proteinuria including microalbuminuria

			<p>using the 4-variable modification of diet in renal disease (MDRD) formula. Clinically meaningful CKD was defined as an eGFR <60 ml/min/1.73m²</p> <p>The most recent serum creatinine and urinary albumin level in the period January 2002 to December 2003 were used for the analysis.</p> <p>GFR was calculated using a validated GFR estimate, the 4-variable modification of diet in renal disease (MDRD) formula (eGFR)</p>		<p>years old.</p> <p>Albuminuria (screening) Albuminuria was determined in only 39.8% of subjects with an eGFR <60 ml/min/1.73m² over the 2-year period of our study despite current recommendations in the UK for annual screening. A greater proportion of subjects (70%) receiving diabetes management in a secondary care setting had albuminuria quantified and this figure is comparable with other diabetes centres. However, this leaves a significant number failing to have any measurement.</p> <p>Diagnostic performance of albuminuria, creatinine >120 µmol to detect an eGFR< 60 ml/min/1.73 m²</p> <p><u>Creatinine > 120 µmol/l</u></p> <table> <tr><td>Sensitivity</td><td>45.3%</td></tr> <tr><td>Specificity</td><td>100%</td></tr> <tr><td>PPV</td><td>100%</td></tr> <tr><td>NPV</td><td>82.8%</td></tr> </table> <p><u>Albuminuria^a</u></p> <table> <tr><td>Sensitivity</td><td>51.2%</td></tr> <tr><td>Specificity</td><td>75.5%</td></tr> <tr><td>PPV</td><td>38.5%</td></tr> <tr><td>NPV</td><td>83.8%</td></tr> </table> <p><u>Creatinine > 120 µmol/l or Albuminuria</u></p> <table> <tr><td>Sensitivity</td><td>82.4%</td></tr> <tr><td>Specificity</td><td>75.4%</td></tr> <tr><td>PPV</td><td>61.7%</td></tr> <tr><td>NPV</td><td>89.9%</td></tr> </table> <p><u>Creatinine > 120 µmol/l and Albuminuria</u></p> <table> <tr><td>Sensitivity</td><td>82.4%</td></tr> </table>	Sensitivity	45.3%	Specificity	100%	PPV	100%	NPV	82.8%	Sensitivity	51.2%	Specificity	75.5%	PPV	38.5%	NPV	83.8%	Sensitivity	82.4%	Specificity	75.4%	PPV	61.7%	NPV	89.9%	Sensitivity	82.4%	
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						<p>Specificity 75.4% PPV 61.7% NPV 89.9%</p> <p><u>Proteinuria</u> Sensitivity 19.4% Specificity 96.1% PPV 57.8% NPV 81.4%</p> <p>Unidentified CKD, defined as the presence of an GFR <60 ml/min/1.73m² but without any evidence of an abnormal creatinine (i.e. serum creatinine ≤120 mmol/l) was significantly greater in females compared with males adjusting for age, type of diabetes and secondary care setting (OR 8.22, CI 6.56 to 10.29).</p> <p>Albuminuria was absent in 52.6% of subjects with CKD stage 3 in whom a measurement was obtained, reinforcing the need for a simple functional measurement of GFR, as provided using the eGFR.</p> <p>Using albuminuria as a screening test also failed to identify CKD in females (OR 2.22, CI 1.63 to 3.03). The presence of abnormal serum creatinine and albuminuria to identify CKD continued to display a significant bias against females (OR 7.58, CI 5.44 to 10.57).</p>	
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T2D , Albuminuria and CKD							
de ZD, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. Kidney International 2004; 65(6):2309-2320 Ref ID: 985	RCT Post-hoc RENAAL	N= 1,513	<p>Inclusion criteria: Participants were considered to have T2D if they were older than 30 years at time of diagnosis of diabetes, had no history of diabetic ketoacidosis, and did not require insulin within 6 months of diagnosis. As an index of nephropathy, urinary ACR >300 mg/g in a first morning void or a 24-hour urine protein >500 mg was defined as an entry criterion. At the time of randomization, patients were stratified according to degree of albuminuria (<2000 mg/g or ≥2000 mg/g). A serum creatinine >1.5 mg/dL in males (>1.3 mg/dL in females or males <60 kg) to 3.0 mg/dL, HbA1c <12%, and an age of 31 to 70 years were also part of the inclusion criteria</p> <p>Exclusion criteria: Patients with T1D or a history of nondiabetic kidney disease were excluded</p>	Losartan vs placebo Follow-up 3 years	Albuminuria ¹⁰ reduction (secondary endpoint)	<p>Baseline albuminuria as a predictor of renal outcome At baseline (total population) Albuminuria was 1.8 g/g creatinine, which is equivalent to a proteinuria of 3 g/day with a range from 0.1 to 15.1 g/day. The degree of proteinuria was comparable with that measured in the subset of patients in whom 24-hour urine was collected (3.4 g/day).</p> <p>Of all the baseline risk markers (age, gender, smoking, ethnicity, weight, blood pressure, cholesterol, serum creatinine, albuminuria, haemoglobin, and HbA1c) albuminuria was by far the strongest predictor of both the renal end point and ESRD:</p> <p>Renal endpoint¹¹: <u>Baseline</u></p> <p>Albuminuria HR 1.41 95%CI (1.36 to 1.47) p< 0.0001 Serum Creatinine HR 1.91 95%CI (1.64 to 2.23) Chi-square: 66.9 p<0.0001 Hemoglobin HR 0.89 95%CI (0.85 to 0.93) Chi-square: 24.5 p<0.0001 HbA1c HR 1.07 95%CI (1.02 to 1.12) Chi-square: 8.9 p= 0.028</p> <p>ESRD <u>Baseline</u></p> <p>Albuminuria HR 1.45 95%CI (1.39 to 1.52) Chi-square: 288.7 p< 0.0001 Serum Creatinine HR 3.51 95%CI (2.83 to 4.36) Chi-square: 130.9 p<0.0001</p>	Merck

¹⁰ Albuminuria was assessed using the ratio of albumin (g/L) to creatinine (g/L) concentrations from a first-morning urine sample

¹¹ The primary efficacy parameter was a composite end point of time to the first event of doubling of serum creatinine, end-stage renal disease (ESRD), or death

						<p>Hemoglobin HR 0.86 95%CI (0.81 to 0.92) Chi-square: 20.0 p<0.0001</p> <p>Kaplan-Meier curves were plotted for renal endpoints for three different baseline albuminuria subgroups. Clearly, the high (≥ 3.0 g/g) as well as the intermediate ($\geq 1.5 < 3.0$ g/g) albuminuria group show significantly more renal events.</p> <p>Comparing the outcomes of patients in the three groups, and when adjusting for baseline risk markers, we found that the renal endpoint was 5.2-fold higher (95% CI 4.3–6.3) in the high versus the low (< 1.5 g/g) albuminuria group. The high albuminuria group had an 8.1-fold (95% CI 6.1– 10.8) increased risk of progressing to ESRD compared to the low albuminuria group.</p> <p>Reduction in albuminuria as a predictor of renal outcome Albuminuria was changed by -14% (95% CI -11% to -17%) in the first 6 months in the total study group, by +4% (95% CI +8 to -1%) in the placebo group, and by -28% (95% CI -25% to -36%) in the losartan group</p> <p>When the total population was subdivided into three groups according to their initial (6 months) reduction in albuminuria ($< 0\%$, $\geq 0 < 30\%$, and $\geq 30\%$), renal events occurred more frequently in the groups that had little to no suppression of albuminuria. In contrast, the groups that had significant reduction in albuminuria showed fewer renal events during follow-up</p> <p><u>Renal endpoint</u></p>	
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