CO-MANAGEMENT OF CKD
Module 2 | Course Notes

RETARDATION OF CKD PROGRESSION

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Proteinuria – Marker for CKD

Normal individuals usually excrete very small amounts of protein in the urine. Persistently increased protein excretion is usually a marker of kidney damage. The excretion of specific types of protein, such as albumin or low molecular weight globulins, depends on the type of kidney disease that is present. The measurement of urinary protein excretion provides a sensitive marker of many types of kidney disease from early to advanced stages.

The identification of persistent proteinuria or albuminuria is important when considering diagnosis, prognosis and therapeutic options. The relative ease with which proteinuria can be assessed and monitored allows clinicians to identify individuals with completely asymptomatic forms of progressive kidney disease during the early stages of their disease.

Since cardiovascular (CV) risks are increased in patients with CKD, more sensitive detection of protein in urine is needed. Evidence is now emerging that CV and all-cause mortality risks are increased at levels within the current ‘normal’ range for urine albumin.

Methods of diagnosis

It is important to consider the timing of urine specimens and the methods for detection of urine proteins. Although the basic concepts of measuring and interpreting urinary protein excretion have changed little over several decades, clinicians must now decide whether simple qualitative or more cumbersome quantitative tests are necessary and whether albumin or total protein should be measured. In clinical practice, most screening methods use a commercial dipstick, which measures total protein or albumin. These dipsticks, which are of course simple to use, usually afford high specificity; ie, they have relatively few false positive results, thereby creating a practical advantage for the clinician. However, they afford low sensitivity; ie, they may fail to detect some forms of kidney disease during the early stages, when the level of proteinuria is below the sensitivity of the test strip used.

Standard urine dipsticks detect total protein above a concentration of 10 to 20 mg/dL. The reagent pad contains a colorimetric pH indicator dye which changes color when bound by negatively charged serum proteins, including albumin and most globulins. The standard urine dipstick is insensitive for low concentrations of albumin that may occur in patients with microalbuminuria. In addition, the standard dipstick is also insensitive to positively charged serum proteins, such as some immunoglobulin light chains.

Albumin-specific dipsticks detect albumin above a concentration of 3 to 4 mg/dL and are useful for detection of microalbuminuria.

Special care should be taken to avoid false negative results which may delay implementation of treatment early in the course of kidney disease.
Timing of urine collection for testing

When screening tests are positive, measurement of protein excretion in a 24-hour collection has been the long-standing “gold standard” for the quantitative evaluation of proteinuria. However, in recent years some studies have shown that the measurement of protein excretion should be done on an overnight specimen. The reason for measuring proteinuria in timed overnight urine collections rather than 24-hour specimens is due to the lack of consistency when hourly protein excretion rates are examined in the same individual at different times during the day. This inconsistency results from varying levels of activity and possibly other factors. But this method poses a problem in individuals with postural (orthostatic) proteinuria—who may excrete more than 1 g of protein during waking hours, but less than 100 mg during sleep. Evaluation for postural proteinuria requires comparison of a measurement of protein excretion in an overnight (“recumbent”) collection to a daytime (“upright”) collection.

An alternative method for quantitative evaluation of proteinuria is measurement of the ratio of protein or albumin to creatinine in an untimed “spot” urine specimen. These ratios correct for variations in urinary concentration due to hydration and provide a more convenient method of assessing protein and albumin excretion than that involved with timed urine collections.

A first morning urine specimen is preferred because it correlates best with 24-hour protein excretion and is required for the diagnosis of orthostatic proteinuria. In children, orthostatic proteinuria must be excluded by a first morning urine protein measurement if the initial finding of proteinuria was obtained on a random specimen during the day. An Australasian Expert Group, the Proteinuria Albuminuria Working Group (PAWG) has proposed that urine albumin/creatinine ratio is measured in a fresh, first morning, spot sample to screen for proteinuria in CKD.2 Otherwise, for ease and consistency of collection, a random urine specimen for protein or albumin to creatinine ratio is acceptable if a first-morning urine specimen is not available.

Total protein versus albumin

The assessment of protein excretion in the urine can be accomplished by several different techniques. In addition to standard methods of measuring total protein, there are now multiple versions of immunoassays capable of detecting albumin levels at concentrations present in the majority of normal people. In general, the literature does not provide substantial information concerning the relative merits of measuring total protein versus albumin to detect and monitor kidney damage. Different guidelines for children and adults reflect differences in the prevalence of specific types of CKD.
In adults, it is preferable to assess proteinuria as albumin, because:
- Albuminuria is a more sensitive marker than total protein for CKD due to diabetes, hypertension, and glomerular diseases.

In adults, the most common types of CKD are due to diabetes, hypertension, and glomerular diseases. In patients with diabetes mellitus, there has been nearly a uniform adoption of albumin as the “criterion standard” in evaluating kidney damage. Thus, for this disease the same standards have been adopted for adults and children. Preliminary data suggest that elevated albumin excretion is also a marker of kidney damage in adults with hypertension. Proteinuria in glomerular diseases is primarily due to increased albumin excretion. Therefore, albumin should be measured to detect and monitor kidney damage in adults.

**Proteinuria in patients with a kidney transplant**

The interpretation of albuminuria in kidney transplant recipients is more complicated than in other patients with CKD.
- First, depending on the interval since transplantation, the patients’ native kidneys may still excrete small amounts of protein, which may be sufficient to elicit a positive result for albumin.
- Second, the main causes of damage in kidney transplant, rejection or toxicity from immunosuppressive drugs, are not characterized by proteinuria. However, diabetic kidney disease is the underlying cause for a large fraction of kidney transplant patients, which may recur in the transplant. Moreover, hypertension is very common after transplantation and is strongly associated with a more rapid loss of kidney function in transplant patients.
- Finally, recurrent glomerular disease may occur after transplantation and is associated with a greater risk of graft loss. Albuminuria is a better marker than total urine protein of kidney damage due to diabetes, hypertension, and glomerular disease. For these reasons, the Work Group recommends testing and monitoring for albuminuria, rather than total protein, in kidney transplant recipients, as well as in patients with other causes of CKD.

The cost or technical difficulty of measuring albumin may exceed that for measuring total protein. It is acceptable to measure total protein-to-creatinine ratio as an index of proteinuria in adults when albumin-to-creatinine ratio is substantially elevated (eg, >500 to 1,000 mg/g). However, there is no reliable method to convert ratios of albumin-to-creatinine to total protein-to-creatinine or vice versa.

**Diabetic nephropathy or DKD and CKD**

Diabetes is a common condition that is very prevalent in the community. In order to give a clear name for the association of kidney disease due to diabetes, the new terminology DKD is followed. Although kidney biopsy is required to confirm diabetic glomerulopathy, careful screening of diabetic patients can, in most cases, identify persons most likely to have diabetic glomerulopathy without the need for a kidney biopsy.\(^3\) DKD is based historically on the finding of proteinuria in a person with diabetes.
With the development of more sensitive assays specific for albumin, DKD is now defined, in part, by increased urinary albumin excretion, which is divided arbitrarily into:

1. microalbuminuria, a modest elevation of albumin thought to be associated with stable kidney function, but a greater risk of macroalbuminuria and kidney failure; and
2. macroalbuminuria, a higher elevation of albumin associated with progressive decline in GFR, an increase in systemic blood pressure, and a high risk of kidney failure.

The table below shows the likelihood of DKD according to GFR and albuminuria levels.

<table>
<thead>
<tr>
<th>GFR (mL/min)</th>
<th>CKD Stage</th>
<th>Albuminuria</th>
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<tr>
<td></td>
<td></td>
<td>Normoalbuminuria</td>
</tr>
<tr>
<td>&gt;60</td>
<td>1+2</td>
<td>At risk†</td>
</tr>
<tr>
<td>30-60</td>
<td>3</td>
<td>Unlikely DKD‡</td>
</tr>
<tr>
<td>&lt;30</td>
<td>4+5</td>
<td>Unlikely DKD‡</td>
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†Because patients with diabetes often have elevated GFR in the early years after diagnosis, GFR less than 90 mL/min may represent a significant loss of function. Kidney biopsy in these patients can show histological evidence of DKD. Patients with diabetes at increased risk of DKD include those with poor glycemic control, longer duration, hypertension, retinopathy, high-normal albuminuria, nonwhite race, and family history of hypertension, CVD, type 2 diabetes, and DKD.

‡Reduction in GFR in patients with diabetes and normoalbuminuria is well described in both type 1 and type 2 diabetes; kidney biopsy in such patients often shows evidence of diabetic glomerulopathy. However, in the absence of histological evidence, these patients should be considered to have diabetes and CKD, which may require further investigation based on the criteria described in this guideline.

However, these generalizations do not apply in all cases because people with normal urinary albumin excretion may have advanced DKD, whereas those with microalbuminuria may have either substantial or no pathological evidence of kidney damage. Moreover, because of the high prevalence of diabetes in the population, some individuals with diabetes may have other types of CKD. Nevertheless, in most cases, clinical measures may be used to diagnose DKD. Most professional societies concerned with diabetes and kidney disease now advocate screening for microalbuminuria in patients with diabetes. Screening should begin after 5 years from the onset of type 1 diabetes and at the time of diagnosis of type 2 diabetes (due to the inability to establish the onset of type 2 diabetes with certainty).
Hypertension

High blood pressure can be either a cause or a consequence of CKD. Adverse outcomes of high blood pressure in CKD include faster decline in kidney function and CV disease. The appropriate evaluation and management of high blood pressure remains a major component of the care of patients with CKD.

- Blood pressure should be closely monitored in all patients with CKD.
- Treatment of high blood pressure in CKD should include specification of target blood pressure levels, nonpharmacologic therapy, and specific antihypertensive agents for the prevention of progression of kidney disease and development of CV disease.

High blood pressure as a cause of end-stage renal disease (ESRD) has increased at an annualized rate of 10% for the last several years, and CV disease is the leading cause of death in ESRD. In part this may be due to inadequate control of high blood pressure in patients with CKD.

High blood pressure is a well-described complication of CKD, with many known causes. The more clinically important pathogenetic mechanisms of high blood pressure are listed in the table below.

<table>
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<th>Table 2. Pathogenetic Mechanisms of High Blood Pressure in Chronic Kidney Disease</th>
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<tr>
<td>Extracellular fluid volume expansion</td>
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<td>Renin-angiotensin aldosterone system stimulation</td>
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<td>Increased sympathetic activity</td>
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<td>Endogenous digitalis-like factors</td>
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<tr>
<td>Prostaglandins/bradykinins</td>
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<td>Alteration in endothelium-derived factors (nitric oxide/endothelin)</td>
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<td>Increased body weight</td>
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<tr>
<td>Erythropoietin administration</td>
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<tr>
<td>Parathyroid hormone secretion/increased intracellular calcium/hypercalcemia</td>
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<tr>
<td>Calcified arterial tree</td>
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<td>Renal vascular disease and renal arterial stenosis</td>
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<tr>
<td>Chronic allograft dysfunction</td>
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<td>Cadaver allografts, especially from a donor with a family history if hypertension</td>
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<tr>
<td>Cyclosporine, tacrolimus, other immunosuppressive and corticosteroid therapy</td>
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In the general population, there is a strong, graded relationship between the level of blood pressure, all-cause mortality and fatal and nonfatal CV disease. Optimal levels of systolic and diastolic blood pressure are defined as less than 120 and 80 mm Hg, respectively. Among patients with CKD, there is also substantial evidence of a relationship between elevated levels of blood pressure and CV risk. In addition, high blood pressure is associated with a greater rate of decline in kidney function and risk of development of kidney failure. However, the optimal level of blood pressure to minimize adverse outcomes for CV and kidney disease has not been established.

Prevalence of high blood pressure is related to the level of GFR. Patients with CKD have a high prevalence of high blood pressure, even when GFR is only mildly reduced. The relationship between GFR and prevalence of hypertension among 1,795 patients was shown in the MDRD Study. At GFR levels of 60 to 90 mL/min/1.73 m², the prevalence of high blood pressure was approximately 65% to 75%. In this study, high blood pressure was defined by patient history (including the use of antihypertensive medications) and medical records, rather than the level of blood pressure. In addition to GFR level, the prevalence of high blood pressure was significantly greater among men and individuals with higher body mass index, black race, and older age. The NHANES III data also shows a similar trend. In NHANES III, the approximately 40% prevalence of high blood pressure among individuals with GFR of approximately 90 mL/min/1.73 m² was lower than in the MDRD Study, presumably because not all patients with GFR in this range in NHANES III had CKD. Among patients with lower GFR, the prevalence of high blood pressure is similar to that observed in the MDRD Study.

Control of hypertension

High blood pressure is not optimally controlled in patients with CKD. A recent analysis of the NHANES III database assessed the level of blood pressure control among individuals with decreased kidney function. Among individuals with decreased kidney function and high blood pressure, 75% received treatment. However, only 11% of individuals with high blood pressure and elevated serum creatinine had blood pressure <130/85 mm Hg, and 27% had blood pressure <140/90. Treated individuals had a mean blood pressure of 147/77 mm Hg, with 48% prescribed only one antihypertensive medication. Thus, it appears that additional efforts will be necessary to lower systolic blood pressure. Multi-drug therapy may be necessary in the majority of patients.

The investigation of antihypertensive agents to prevent or delay the progression of CKD and development of CV disease is a rapidly evolving. A number of guidelines and recommendations have been developed.

Detection, evaluation and management of high blood pressure should be the goal for all health care providers for patients with CKD. Providers must be aware of lower recommended target levels for blood pressure for patients with CKD, specific recommendations for classes of antihypertensive agents, and the role of nonpharmacologic therapy.

References:
Laboratory measurement of urine albumin and urine total protein in screening for proteinuria in chronic kidney disease.

Martin H.

Source
Department of Biochemistry, Healthscope Pathology, Wayville, SA 5034, Australia.

Abstract
Laboratory measurement of urine total protein has been important for the diagnosis and monitoring of renal disease for decades, and since the late 1990s, urine albumin has been measured to determine whether a diabetic patient has incipient nephropathy. Evolving understanding of chronic kidney disease (CKD) and, in particular, the cardiovascular risks that CKD confers, demands more sensitive detection of protein in urine. As well, evidence is now emerging that cardiovascular and all-cause mortality risks are increased at levels within the current ‘normal’ range for urine albumin. Standardization is essential to permit valid application of universal decision points, and a National Kidney Disease Education Program/International Federation of Clinical Chemistry and Laboratory Medicine (NKDEP/IFCC) Working Party is making progress towards a reference system for urine albumin. In the meantime, available data suggest that Australasian laboratory performance is adequate in terms of precision and accuracy above current decision limits for urine albumin. In contrast, the complexity of proteins in urine makes standardization of urine total protein measurement impossible. As well, urine total protein measurement is insufficiently sensitive to detect clinically important concentrations of urine albumin. An Australasian Expert Group, the Proteinuria Albuminuria Working Group (PAWG) has proposed that urine albumin/creatinine ratio is measured in a fresh, first morning, spot sample to screen for proteinuria in CKD. Both NKDEP/IFCC and PAWG emphasize the need for standardization of sample collection and handling.

Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality.


Source
Department of Medicine, San Francisco VA Medical Center, San Francisco, California, USA. carmenalicia.peralta@ucsf.edu

Abstract
CONTEXT:
A triple-marker approach for chronic kidney disease (CKD) evaluation has not been well studied.

OBJECTIVE:
To evaluate whether combining creatinine, cystatin C, and urine albumin-to-creatinine ratio (ACR) would improve identification of risks associated with CKD compared with creatinine alone.

DESIGN, SETTING, AND PARTICIPANTS:
Prospective cohort study involving 26,643 US adults enrolled in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study from January 2003 to June 2010. Participants were categorized into 8 groups defined by estimated glomerular filtration rate (GFR) determined by creatinine and by cystatin C of either <60 or ≥60 mL/min/1.73 m² and ACR
of either <30 or ≥30 mg/g.

**MAIN OUTCOME MEASURES:**
All-cause mortality and incident end-stage renal disease with median follow-up of 4.6 years.

**RESULTS:**
Participants had a mean age of 65 years, 40% were black, and 54% were women. Of 26,643 participants, 1940 died and 177 developed end-stage renal disease. Among participants without CKD defined by creatinine, 24% did not have CKD by either ACR or cystatin C. Compared with those with CKD defined by creatinine alone, the hazard ratio for death in multivariable-adjusted models was 3.3 (95% confidence interval [CI], 2.0-5.6) for participants with CKD defined by creatinine and ACR; 3.2 (95% CI, 2.2-4.7) for those with CKD defined by creatinine and cystatin C, and 5.6 (95% CI, 3.9-8.2) for those with CKD defined by all biomarkers. Among participants without CKD defined by creatinine, 3863 (16%) had CKD detected by ACR or cystatin C. Compared with participants who did not have CKD by any measure, the HRs for mortality were 1.7 (95% CI, 1.4-1.9) for participants with CKD defined by ACR alone, 2.2 (95% CI, 1.9-2.7) for participants with CKD defined by cystatin C alone, and 3.0 (95% CI, 2.4-3.7) for participants with CKD defined by both measures. Risk of incident end-stage renal disease was higher among those with CKD defined by all markers (34.1 per 1000 person-years; 95% CI, 28.7-40.5 vs 0.33 per 1000 person-years; 95% CI, 0.05-2.3) for those with CKD defined by creatinine alone. The second highest end-stage renal disease rate was among persons missed by the creatinine measure but detected by both ACR and cystatin C (rate per 1000 person-years, 6.4; 95% CI, 3.6-11.3). Net reclassification improvement for death was 13.3% (P < .001) and for end-stage renal disease was 6.4% (P < .001) after adding estimated GFR cystatin C in fully adjusted models with estimated GFR creatinine and ACR.

**CONCLUSION:**
Adding cystatin C to the combination of creatinine and ACR measures improved the predictive accuracy for all-cause mortality and end-stage renal disease.

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Eur Heart J. 2011 Mar 28. [Epub ahead of print]

**Renal function and target organ damage in hypertension.**
Ruilope LM, Bakris GL.

**Source**
Hypertension Unit, Hospital 12 de Octubre, 28041 Madrid, Spain.

**Abstract**
Chronic kidney disease (CKD) is frequently observed in patients with arterial hypertension. The same factors that promote the appearance and progression of atherosclerosis can also promote the development of CKD. Two parameters are usually measured to estimate alterations in renal function, the presence of albuminuria, and the estimation of glomerular filtration rate (GFR). Microalbuminuria and a decreased estimated GFR (<60 mL/min/1.73 m²) are both accompanied by a significant increase in cardiovascular (CV) risk. Chronic kidney disease can develop all over the cardiorenal continuum and its presence in hypertensive patients with already developed CV disease contributes to a further increase in the development of events and death. Renal protection will in turn obtain CV protection and the treatment to be used is similar to that employed to prevent or to treat established CV disease.
ABSTRACTS

Diabetic kidney disease with and without albuminuria.
Macisaac RJ, Jerums G.

Source
Endocrine Centre, Austin Health and University of Melbourne, Heidelberg West, Victoria, Australia. r.macisaac@unimelb.edu.au

Abstract

PURPOSE OF REVIEW:
Historically, for people at risk of developing diabetic chronic kidney disease (CKD), an initial increase in albumin excretion rate (AER) has been linked to a subsequent decline in glomerular filtration rate (GFR). We review recent findings that suggest that in some people with diabetic CKD there is an uncoupling of progressive increases in AER and declining GFR.

RECENT FINDINGS:
Approximately 20% of people with type 2 diabetes develop at least stage 3 CKD, defined as an estimated GFR (eGFR) less than 60 ml/min/1.73 m², after accounting for the use of renin-angiotensin system blockers, while remaining normoalbuminuric. A recent analysis from the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications study has shown that 24% of people with type 1 diabetes reached an eGFR threshold of less than 60 ml/min/1.73 m² that was not associated with a rise in albuminuria to the microalbuminuria or macroalbuminuria range. This discordance between changes in GFR and AER has resulted in a search for new markers that identify people with diabetes who are at risk of declining GFR independent of progressive increases in AER.

SUMMARY:
The conventional paradigm of kidney disease in people with diabetes has been challenged. Changes in AER and GFR are being increasingly recognized as complementary rather than obligatory manifestations of diabetic CKD.

Consensus document. Recommendations on assessing proteinuria during the diagnosis and follow-up of chronic kidney disease.

Montañés Bermúdez R, Gràcia García S, Pérez Surribas D, Martínez Castelao A, Bover Sanjuán J.

Abstract

The presence of persistently high urinary concentrations of protein or albumin is considered a sign of kidney damage. Nowadays, the diagnosis of chronic kidney disease (CKD) is based on the presence of signs of kidney damage together with the estimation of the glomerular filtration rate. The presence of either proteinuria or albuminuria identifies a group of patients with a higher risk of progression of CKD and higher cardiovascular risk. Treatment with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers decreases both the progression of CKD and the incidence of cardiovascular events and death in patients with CKD and proteinuria. Thus, proteinuria is currently considered a therapeutic target by itself. Despite the importance of detecting and monitoring proteinuria in the diagnosis and follow-up of CKD, there is no consensus among the clinical practice guidelines published by different scientific societies on the diagnostic cut-off levels, on different sampling procedures, on the units used in laboratory reports or just
on whether it should be defined in terms of albuminuria or proteinuria. The goal of this document, created with the agreement of the Spanish Society of Clinical Biochemistry and Molecular Pathology (SEQC, representing its Spanish acronym) and the Spanish Society of Nephrology (S.E.N.), is to recommend appropriate guidelines to medical and laboratory physicians for detecting and monitoring proteinuria as a marker of CKD in adults and children. These recommendations are the result of searching, evaluating and summarising current scientific evidence published in the last few years.

QJM. 2011 Jun 6. [Epub ahead of print]

_Estimating glomerular filtration rate: comparison of the CKD-EPI and MDRD equations in a large UK cohort with particular emphasis on the effect of age._ Carter JL, Stevens PE, Irving J, Lamb EJ.

**Source**
From the Clinical Biochemistry and Kent Kidney Care Centre, East Kent Hospitals University NHS Foundation Trust, Canterbury, Kent, UK.

**Abstract**

**BACKGROUND:**
The chronic kidney disease (CKD)-Epidemiology Collaboration (CKD-EPI) equation was developed to address the underestimation of measured glomerular filtration rate (GFR) by the Modification of Diet in Renal Disease (MDRD) equation at levels >60 mL/min/1.73 m².

**AIM:**
To assess the impact of the CKD-EPI equation on the estimation of GFR in a large adult UK population (n=561 400), particularly looking at the effect of age.

**DESIGN:**
Serum creatinine results (ID-MS-aligned enzymatic assay) were extracted from the pathology database during 1 year on adult (≥18 years) patients from primary care.

**METHODS:**
The first available creatinine result from 174 448 people was used to estimate GFR using both equations and agreement assessed.

**RESULTS:**
Median CKD-EPI GFR was significantly higher than median MDRD GFR (82 vs. 76 mL/min/1.73 m², P<0.0001). Overall mean bias between CKD-EPI and MDRD GFR was 5.0%, ranging from 13.0% in the 18-29 years age group down to -7.5% in those aged ≥90 years. Although statistically significant at all age groups the difference diminished with age and the agreement in GFR category assignment increased. Age-adjusted population prevalence of CKD Stages 3-5 was lower by CKD-EPI than by MDRD (4.4% vs. 4.9%).

**CONCLUSION:**
CKD-EPI produces higher GFR and lower CKD estimates, particularly among 18-59 year age groups with MDRD estimated GFRs of 45-59 mL/min/1.73 m² (Stage 3A). However, at ages >70 years there is very little difference between the equations, and among the very elderly CKD-EPI may actually increase CKD prevalence estimates.

Intensive glycemic control and renal outcome.
Jun M, Perkovic V, Cass A.

Source
Renal and Metabolic Division, The George Institute for Global Health, Sydney Medical School, University of Sydney, Camperdown, N.S.W., Australia.

Abstract
Diabetes is the leading cause of chronic kidney disease (CKD) in many countries around the world, accounting for up to 50% of people who develop end-stage renal disease. The risk of morbidity and mortality is particularly high in people with both conditions, highlighting the importance of preventing the development and progression of earlier stage CKD in people with diabetes. Inadequate glycemic control has been associated with poor outcomes in diabetes, with early observational studies suggesting that tighter glycemic control may improve microvascular and macrovascular outcomes in patients with diabetes. Since then, large trials assessing the effect of intensive glycemic control in the general diabetic population have provided strong evidence that intensive therapy reduces the incidence and progression of microvascular outcomes including microalbuminuria, a key early marker of diabetic nephropathy (DN). These results have been consistent across both type 1 and type 2 diabetic populations demonstrating that intensive glycemic therapy provides clear benefits, delays the onset or progression of DN, particularly in its early stages. Whilst the benefits of intensive glycemic therapy for people with diabetes and early stage CKD have been well established, controversy remains as to whether intensive therapy slows the progression of established DN, particularly among individuals who have a reduced glomerular filtration rate. In addition, severe hypoglycemia has been associated with intensive glycemic therapy, raising safety concerns that may be of particular relevance for patients with decreased kidney function (CKD stages 3-5). Until further data are available, an individualized approach to glucose management is recommended in people with reduced glomerular filtration rate.


Diabetic tubulopathy: an emerging entity.
Tang SC, Leung JC, Lai KN.

Source
Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong SAR, China.

Abstract
In chronic glomerulopathic disease, renal function correlates more with the degree of tubulointerstitial injury than that of the glomerular lesions. Proteinuria may be one of the pathologic links between these two intrarenal compartments. It is apparent that the proximal tubular epithelial cell (PTEC) assumes a proinflammatory and profibrotic role during proteinuria in which the PTEC expresses a variety of chemokines and injury signals that culminate in progressive interstitial inflammation and fibrosis. During diabetes, other substrates including advanced glycation end products (AGEs), AGE intermediates, and high glucose (HG) may provoke the PTEC even further. Glycated albumin, but not the equivalent dose of bovine serum albumin (BSA), stimulates tubular IL-8 and ICAM-1 expression via NF-κB-, MAPK- and STAT-1-dependent pathways. Human biopsies of diabetic nephropathy (DN) reveal colocalization of AGE and ICAM-1 in proximal tubules. The biologically active carbonyl intermediates methylglyoxal-BSA-AGE and AGE-BSA upregulate tubular
expression of CTGF, TGF-β, and VEGF, whereas carboxymethyllysine-BSA stimulates tubular expression of IL-6, CCL-2, CTGF, TGF-β, and VEGF via RAGE activation and NF-κB signal transduction. Hyperglycemia (30 mM), but not the equivalent dose of mannitol, promotes proinflammatory (IL-6 and CCL-2), profibrotic (TGF-β) and angiogenic (VEGF) responses in tubular cells via MAPK and PKC signaling and induces epithelial mesenchymal transition, which is TGF-β1 mediated. It has recently been shown that toll-like receptor (TLR) is implicated in the diabetic kidney. In human DN biopsies and PTEC, TLR4 is upregulated and plays a permissive role in HG-induced IL-6 and CCL-2 overexpression and monocyte transmigration. In streptozotocin-induced rat DN and PTEC, TLR2 appears to be upregulated. Other novel mediators that become activated in PTEC exposed to HG include macrophage inflammatory protein-3-α, Krüppel-like factor 6 and thioredoxin-interacting protein, which may be attenuated by peroxisome proliferator-activate d receptor-γ activation. Collectively, these phenomena suggest that the renal tubules are heavily involved in the pathogenesis of DN. These pathophysiologic responses may be collectively described as diabetic tubulopathy.


Renal function in diabetic nephropathy.
Dabla PK.

Source
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Abstract
Diabetic nephropathy is the kidney disease that occurs as a result of diabetes. Cardiovascular and renal complications share common risk factors such as blood pressure, blood lipids, and glycemic control. Thus, chronic kidney disease may predict cardiovascular disease in the general population. The impact of diabetes on renal impairment changes with increasing age. Serum markers of glomerular filtration rate and microalbuminuria identify renal impairment in different segments of the diabetic population, indicating that serum markers as well as microalbuminuria tests should be used in screening for nephropathy in diabetic older people. The American Diabetes Association and the National Institutes of Health recommend Estimated glomerular filtration rate (eGFR) calculated from serum creatinine at least once a year in all people with diabetes for detection of kidney dysfunction. eGFR remains an independent and significant predictor after adjustment for conventional risk factors including age, sex, duration of diabetes, smoking, obesity, blood pressure, and glycemic and lipid control, as well as presence of diabetic retinopathy. Cystatin-C (Cys C) may in future be the preferred marker of diabetic nephropathy due differences in measurements of serum creatinine by various methods. The appropriate reference limit for Cys C in geriatric clinical practice must be defined by further research. Various studies have shown the importance of measurement of albuminuria, eGFR, serum creatinine and hemoglobin level to further enhance the prediction of end stage renal disease.
Abstract
Lowering blood pressure may confer a benefit to diabetic microvascular complications comparable with glycemic control. Hypertension is causally related to kidney outcomes and is a risk factor for the development of diabetic retinopathy. The prevalence of hypertension increases as kidney disease progresses, so that it coexists with diabetes in up to 80% of those with overt nephropathy. A significant number of patients have hypertension or rising blood pressures in earlier stages, or even before microvascular complications appear. Because microalbuminuria markedly increases the risk of overt nephropathy as well as of cardiovascular complications, primary prevention (i.e., preventing or delaying the onset of microalbuminuria) continues to be explored, predominantly through use of renin-angiotensin blockade. Available data reviewed suggest that primary prevention through blood pressure reduction is more likely to benefit select groups (those with hypertension, cardiovascular risks, or old age). This review discusses the relationship between hypertension, diabetes, and kidney disease, the rationale for primary prevention, and the data that led to that conclusion.
Targeting the renin angiotensin system in dialysis patients.
Cravedi P, Remuzzi G, Ruggenenti P.

Source
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Abstract
Patients on chronic dialysis therapy have a dramatic excess cardiovascular risk compared to any other population, including those with overt diabetic nephropathy. Despite this, patients on dialysis are almost invariably excluded from trials evaluating the cardioprotective effect of novel treatments. Consistent evidence is available that inhibitors of the renin-angiotensin system, such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), are more cardioprotective than other antihypertensive agents in patients with chronic renal disease or diabetes (with or without renal involvement), but whether this applies also to patients on dialysis is unknown. However, clear evidence is available that ACE inhibitors and ARBs reduce morbidity and mortality in patients on dialysis with heart failure (HF) or atrial fibrillation (AF). Moreover, these drugs may preserve residual renal function in those with preterminal kidney failure as well as vascular access and peritoneal membrane function in those on extracorporeal or peritoneal dialysis, respectively. These drugs also show an excellent tolerability profile in this population. Thus, ACE inhibitors and ARBs are indicated in patients on dialysis with HF or AF. Available evidence suggests that they should be first-choice therapy in patients on dialysis with hypertension, though trials are still needed to formally demonstrate their superior cardioprotective effect over other antihypertensives in this population.