Use and Interpretation of Urinary Albumin and Estimated Glomerular Filtration Rate Findings in Primary Health Care

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Use and Interpretation of Urinary Albumin and Estimated Glomerular Filtration Rate Findings in Primary Health Care

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When I was a child my grandfather used to gather the family together during springtime so that we could collect the stones that had been uncovered by ploughing the soil on our farmland. This hard work, boring and never-ending, turned out to be a very useful experience when later coincidences in life brought me to work in research; I learned that you are able to finish any overwhelming or seemingly endless project if you have an inspiring and encouraging mentor, and that even the most boring work can be great fun if performed with good co-workers. I learned that even if you get frustrated, you must respect your co-workers because we all depend upon each other, and after a short while we will be laughing together again. Finally, I learned that you need someone to take care of you who can fill your breaks with joy and laughter. So what more is there to say?

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Foreword

The daily work of physicians includes a constant flow of information: diagnostic tests or drugs that are marketed for various and sometimes changing indications, and new and/or rare clinical diagnoses that should be noticed or unexpected manifestations of already well-known diseases that need to be acknowledged. Physicians also need to keep up with a large number of continuously changing regulations regarding the social aspects of health care. In this context, it is understandable that laboratories can experience difficulties informing physicians about the introduction of new laboratory tests or about changes in the use of well-known tests, which could involve changes regarding when or how to perform the test or how to interpret the results. Given that the correct diagnosis and follow-up of patients will ultimately always be the responsibility of that patient's physician, what is the responsibility of the laboratory? There are of course many answers to this question, but the data presented in this dissertation focuses on one main aspect: the responsibility of the laboratory to help physicians to choose the best available test procedures, and to get the most out of the information provided by the test results, thereby facilitating the correct diagnosis and follow-up of patients.

During recent years the indications for some renal parameters have changed, and new tests have been introduced to facilitate the earlier diagnosis of renal disease (e.g. albumin:creatinine ratio and estimated glomerular filtration rate). Common practice is to implement such changes only after limited information programmes and to report laboratory results without comments. We chose to investigate how these tests are used and interpreted in the primary health-care setting. Our findings may be generally applicable to situations where changes in other laboratory analyses are implemented in similar ways. After investigating current practices and the possible consequences of misinterpretations, we have been able to introduce some initiatives that may improve laboratory practice and the understanding of laboratory test results in the future, making information more accessible to physicians.

Abstract

Aims: Chronic kidney disease (CKD) affects approximately 10% of the adult population. CKD patients have increased risks of morbidity and mortality, mainly from cardiovascular end points; early diagnosis and treatment is therefore warranted. CKD may be diagnosed based on an estimated glomerular filtration rate (eGFR) that is calculated from creatinine data, and the prognosis may be predicted based on urinary albumin excretion. The aim of this work was to elucidate how urinary albumin and eGFR are used and interpreted in the primary health-care setting. Another focus was to assess how the clinical chemistry laboratories that usually offer these tests interpret the test results.

Methods: In all four studies, data were collected with the aid of a questionnaire. For Articles I and II, 10,000 general practitioners in 11 countries received a case-history-based questionnaire depicting a male type 2 diabetes patient. For Article III, 386 physicians received a questionnaire asking about 1 of their patients (selected from 2 different hospital laboratory databases) who had been diagnosed with CKD stage 3, based on eGFR results. For Article IV, 100 laboratory specialists in Norway and the Netherlands received a questionnaire regarding 2 case histories from primary health care (hypertensive and diabetic patients with laboratory results signalling possible renal disease) and 1 from a hospital setting.

Results: The studies described in Articles I and II included 2078 general practitioners from 9 European countries. Almost all of the general practitioners recommended annual microalbuminuria testing in diabetic patients, whilst a lower frequency of testing was suggested for patients with hypertension or possible CKD. A spot urine sample prevailed for first-time office-based testing, whilst timed collections were used to a larger extent for hospital-based repeat testing. Of the 2078 general practitioners, 62% requested a repeat test to confirm the diagnosis if the first test was positive. Median values for the critical difference in albumin values was 33%, and four different measurement units were used. The absolute increase in the percentage of general practitioners who would supplement the patient's drug treatment if

microalbuminuria developed was 23–50% (depending on the country) for angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), 0–19% for statins, 2–13% for acetylsalicylic acid and 0–33% for hypoglycaemic agents (tablets and insulin). For Article III, the response rate was 60%, and 210 patients were included. The median creatinine values were 95 and 124 µmol/l for female and male patients; the corresponding eGFR values were 52 and 51 ml/min/1.73m^2. Only 27% of patients were assessed to have CKD stage 3. Two-thirds had a urine dip strip (59%) and/or a urinary albumin (42%) measurement, and 20% were diagnosed with albuminuria (including both micro- and macroalbuminuria). Median changes to signal improvement or deterioration in renal function or indicating need for referral were 14 (12%), 20 (18%), and 40 (36%) µmol/l, respectively, for creatinine, and 8 (17%), 8 (17%) and 13 (26%) ml/min/1.73 m^2 for eGFR. Albuminuria did not influence the follow-up strategy. For Article IV, 52 (52%) laboratory specialists responded. Based on guideline recommendations, less than 30% would suggest an optimal test panel for evaluating renal function in the two primary-care patients. For creatinine and eGFR, the median changes considered to signal improvement or deterioration in renal function (creatinine, 14% and 14%, respectively; eGFR, 18% and 13%, respectively) were similar to what could be calculated using information on analytical and within-subject variations from the literature. The albumin:creatinine ratio varied (median values: 50% for improvement and 67% for deterioration).

Conclusions: Guidelines for diagnosing microalbuminuria are only partially followed by general practitioners, and should be made more practicable, addressing issues such as type of samples, measurement units and repeat tests. Intensified drug treatment, and especially increased use of ACEIs and ARBs, was recommended to diabetic patients when microalbuminuria was present. CKD stage 3 patients were insufficiently examined for albuminuria and seemingly referred to hospital care only after the eGFR declined more than recommended in guidelines. Renal parameters are interpreted differently by laboratory specialists, and this could result in different advice being offered to clinicians, which again may affect patient care.

Contents

LIST OF PUBLICATIONS

I. Kristin M. Aakre, Geir Thue, Sumathi Subramaniam-Haavik, Tone Bukve, Howard Morris, Mathias Müller, Marijana V. Lovrencic, Inger Plum, Kaja Kallion, Alar Aab, Marge Kutt, Phillipe Gillery, Nathalie Schneider, Andrea R. Horvath, Rita Onody, Wytze Oosterhuis, Carmen Ricos, Carmen Perich, Gunnar Nordin and Sverre Sandberg: Postanalytical external quality assessment of urine albumin in primary health care: an international survey. Clin Chem 2008; 54(10):1630–6.

II. Kristin M. Aakre, Geir Thue, Sumathi Subramaniam-Haavik, Tone Bukve, Howard Morris, Mathias Müller, Marijana V. Lovrencic, Inger Plum, Kaja Kallion, Alar Aab, Marge Kutt, Phillipe Gillery, Nathalie Schneider, Andrea R. Horvath, Rita Onody, Wytze Oosterhuis, Carmen Ricos, Carmen Perich, Gunnar Nordin and Sverre Sandberg: Diagnosing microalbuminuria and consequences for the drug treatment of patients with type 2 diabetes: a European survey in primary care. Diabetes Res Clin Pract 2010; 89(2):103–9.

III. Kristin M. Aakre, Geir Thue, Einar Svarstad, Øyvind Skadberg and Sverre Sandberg: Laboratory investigation and follow-up of chronic kidney disease stage 3 in primary care. Clin Chim Acta 2011, in press
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ABBREVIATIONS

ACEI: angiotensin-converting enzyme inhibitor

ACR: albumin:creatinine ratio

ARBs: angiotensin II receptor blocker

ASA: acetylsalicylic acid

CD: critical difference

CKD: chronic kidney disease

CVa: analytical variation

CVD: cardiovascular disease

CVi: within-subject biological variation

CVg: between-subject biological variation

eGFR: estimated glomerular filtration rate

ESRD: end-stage renal disease

GFR: glomerular filtration rate

GP: general practitioner

MDRD: Modification of Diet in Renal Disease

POCT: point-of-care testing

INTRODUCTION

The following second-level sections provide the background on chronic kidney disease (CKD), biological variations and critical differences (CDs), and describe the use of biomarkers in renal disease, with special emphasis on measurements of urinary albumin and the estimated glomerular filtration rate (eGFR). Furthermore, how laboratories communicate with clinicians and how questionnaires may be used as a research tool are discussed.

Chronic kidney disease

Definition of chronic kidney disease

CKD is defined by the patient's glomerular filtration rate (GFR) and markers of renal injury, and according to the Kidney Disease Quality Outcome Initiative classification may be divided into five different stages (Table 1) (1). This classification system has now been adopted by most medical societies (2-7). Stages 1 and 2 require urine examination for albuminuria, proteinuria or haematuria, whilst stages 3–5 are defined only by GFR values. GFR measurements should be obtained on two occasions separated by at least 3 months when determining whether to classify the condition as chronic. Stage 5 is defined as end-stage renal disease (ESRD) or kidney failure, and usually requires dialysis therapy.

Table 1. Definition and staging of CKD.

Stage	Description	GFR (ml/min/1.73 m^2)
1	Kidney damage* with normal or increased GFR	≥90
2	Kidney damage* with mild reduction in GFR	60–89
3	Moderate reduction in GFR	30–59
4	Severe reduction in GFR	15–29
5	Kidney failure (ESRD)	<15 (or dialysis)

*Defined as albuminuria, proteinuria, haematuria, or anatomical abnormality

The CKD classification system has been criticized for not being sufficiently accurate and labelling patients without progressive kidney disease as having moderately reduced renal function (8, 9). Even if a rapid decline in GFR (a decrease over 1 year of 4–5 ml/min/1.73 m^2) signals a worse prognosis of CKD, the course of the disease may usually be predicted by the finding of albuminuria or proteinuria (10-13) that is seen in approximately 30% of CKD stage 3 patients (14). It has therefore been suggested that albuminuria assessment should be included in the classification of CKD (15, 16) for the purpose of targeted follow-up and treatment of patients at higher risk. eGFR values in the range of 50–60 ml/min/1.73 m^2 are quite common in healthy subjects older than 70 years (9). Thus, it has also been suggested that stage 3 should be subdivided into two stages, 3A (GFR 45–59 ml/min/1.73 m^2) and 3B (GFR 30–44 ml/min/1.73 m^2), which could yield more information in epidemiological studies (17) and better differentiate between patients with a stable low renal function and those at greater risk of progressive renal disease.

Epidemiology of chronic kidney disease

Recent studies have shown CKD to be far more common in the adult population than was previously expected. More than 10% of the adult population may be affected (14, 18), and newer data suggest that the prevalence is increasing (19, 20). Most patients (about 50%) are classified as CKD stage 3. The prevalence of CKD increases with age and is more frequent among females (21), whilst the dialysis departments are frequently populated by males (22, 23). Important risk factors for developing CKD are hypertension (24), which affects most patients at CKD stage 3 or lower, and diabetes, which affects 10–20% of the overall CKD population (21). Cardiovascular disease (CVD) is found in 15–50% of CKD patients (21, 25, 26), with the prevalence increasing as renal function deteriorates. The risk of developing ESRD is much lower than the mortality risk during the course of the disease (10); one study found that only 1% of CKD stage 3 patients progressed to renal replacement therapy during a 5-year follow-up, whilst 24% died during the observation period (27). A British study

showed that 4% of patients with creatinine levels of ≥150 µmol/l developed ESRD during a 5.5-year follow-up, whilst 69% died during the observation period, mostly from cardiovascular end points (28). Even so, 700–800 adults per million of the European population receive renal replacement therapy (i.e. dialysis, haemofiltration or transplantation), and the incidence is increasing (22, 23).

Renal disease in diabetes

Diabetes is a chronic disease whose prevalence is increasing rapidly. The World Health Organization estimates that by 2030 about 350 million people worldwide will suffer from the disease, and mainly type 2 diabetes (29). Diabetic patients are at increased risk of CVD and microvascular complications, retinopathy, neuropathy and nephropathy. The prevalence of diabetic nephropathy is related to the duration of diabetes and glycaemia control, and reportedly lies in the range 12–40% (30, 31). Diabetic nephropathy is defined as albuminuria (i.e. a raised urinary albumin excretion above 300 mg/day), corresponding to an albumin:creatinine ratio (ACR) of approximately 30 mg/mmol; renal damage is considered to be irreversible at this stage. To facilitate earlier diagnosis and treatment, and thereby prevent diabetic nephropathy from developing, annual screening to detect lower concentrations of urinary albumin (30–299 mg/day) has been recommended for decades (32). A low concentration of urinary albumin (often referred to as microalbuminuria) is an independent predictor of CVD and ESRD (33), but the risks are reduced if adequate treatment is provided, mainly by reducing blood pressure and lowering blood glucose (34-36). This is further discussed later in this dissertation (see page 25, “Interpretation of urinary albumin results”).

Screening for chronic kidney disease

The early stages of renal disease cause few and vague symptoms, and most CKD patients will therefore not seek medical treatment (37). General screening programmes or screening in high-risk populations have been discussed, and current guidelines recommend eGFR and urinary albumin (or protein) examinations in patients with hypertension, diabetes, CVD or at risk of CVD, and in patients with a family history of CKD (4-6, 38-43).

There are several benefits of diagnosing CKD at its early stages (i.e. stages 1–3): the patients may receive intensified treatment for hypertension and hyperglycaemia (diabetic patients), and complications (i.e. anaemia and bone-related renal disease) (6) may be treated earlier. Monitoring urinary albumin is useful for guidance during the follow-up period (6, 44-47). Mortality rates are 10–20 times higher among dialysis patients than in the general population (48); 20–30% of patients are referred to nephrology care less than 90 days before starting dialysis (22, 49), and it has been shown that late referral is a risk factor that can increase mortality even further (50). CKD patients are at increased risk of developing acute renal failure during acute illness. If CKD is not recognized delayed renal protective treatment in these situations may lead to a permanent need for renal replacement therapy (51). Earlier identification of CKD is therefore an important issue both for the individual patient and for society. Targeted surveillance aims at delaying the progression of renal disease and reducing the associated mortality, morbidity and the need for renal replacement therapy (6, 34-36), leading to improved quality of life and a reduced financial burden on the health-care system.

INTERPRETATION OF CHANGES IN LABORATORY TEST RESULTS

Biological variation

Biological variation is defined as natural fluctuations in the concentrations of constituents around a homeostatic set point, and both the within-subject biological variation (CVi) and between-subject biological variation (CVg) may be calculated based on data from repeated sampling. Data on the biological variations for different biomarkers have been published (52) and are also available on Westgard's homepage (53). Even so, these data need to be interpreted with caution, since not all have been obtained using a strict methodology (54). It is therefore crucial that reports on biological variations strictly define the methods used to obtain the data (e.g. exclusion of outliers, tests for homogeneous variances and pre-analytical conditions such as sampling time, posture, centrifugation, type of specimen used, time of measurement and storage of the samples before measurement).

Biological variation can be used to define analytical quality specifications, calculating the CD (see below for further explanation) between follow-up results and for calculating the index of individuality to determine whether population-based reference values are suitable for detecting pathological changes (55). The index of individuality is defined as CVi/CVg; values lower than 0.6 are normally indicative of a large population-based reference range, which are of lesser value as action limits for detecting pathological results in individual patients; therefore, CD values may be used instead. When the index of individuality exceeds 1.4 (corresponding to a large CVi and small CVg, comparison with reference ranges is more likely to reveal significant changes in patients' test results, and so this parameter is considered more useful. Between these two cut-off values is a grey zone wherein both the application of reference ranges and CD values may be useful for defining action limits.

Critical difference and diagnostic cut-off values

Clinically important changes in biomarker concentrations may be evaluated using the concept of CD described by Fraser and Harris in 1989 (55). The CD is defined as the minimum difference needed between two consecutive results to be certain (with a specified level of confidence, *z*) that the results are truly different, and that the difference is not only due to analytical variation (CVa) and CVi (55):

$$CD = bias + z \times \sqrt{2} \times \sqrt{CVa^2 + CVi^2}$$

The value of *z* defines the level of confidence when calculating the CD. The *bias* value denotes differences due to samples being analysed at different times (e.g. due to calibrations or different reagent lots) and may be included in the CVa (imprecision under reproducibility conditions). It is important to emphasize that the CD value only provides a measure for judging the probability that a change between consecutive results may be explained on the basis of CVa and CVi for a patient in a stable situation; it does not provide a measure with which to judge the probability that a true change (deterioration or improvement) has occurred. It is important to take both of these aspects into account when fully evaluating the difference between two results (56).

BIOMARKERS IN CHRONIC KIDNEY DISEASE

Biomarkers in renal disease may be divided into two categories: (i) those measuring GFR and (ii) those detecting renal injury through urine analysis. GFR is measured as the renal clearance (i.e. measurement of the rate of renal filtration of a substance freely filtered by the glomerulus and not excreted or reabsorbed in the renal tubules).

The gold-standard clearance method used to be that of inulin. This is a cumbersome procedure involving several serum and urine samplings and has for practical purposes been replaced by simpler methods whose results correlate strongly with inulin clearance. Examples are the clearances of iohexol and iothalamate (contrast media), and of ^{51}Cr-EDTA and ^{99}Tc-DPTA (radioisotopes) (57, 58). Formulas that correct for the extracellular distribution of the injected substance are normally used when calculating the results (59, 60), so that only one blood sample needs to be obtained after injecting the substance. Even though the procedure has been simplified, it is still invasive and usually only used when precise GFR measurements are needed (e.g. when evaluating kidney donors or patients receiving nephrotoxic drugs for a long time) (5, 6). The GFR may also be calculated (i.e. estimated) based on concentrations of in-vivo biomarkers for renal disease; a more detailed description of such algorithms is given later in this dissertation (See page 26, “Estimating the glomerular filtration rate”).

The common method for evaluating renal function in primary health-care and most hospital settings is the measurement of different metabolites produced in vivo, freely filtered by the glomerulus and then to various degrees reabsorbed or excreted in the renal tubules. Such parameters are influenced by different physiological processes and therefore can be inaccurate measures of renal function. Creatinine is produced at fixed rates, since 1–2% of creatine phosphate in muscle is converted into creatinine daily, and therefore the actual amount of creatinine produced (i.e. the concentration of creatinine) will vary greatly between subjects due to differences in muscle mass. In addition, decreases in renal function lead to increased excretion of creatinine in the renal tubules. Urea is produced during protein metabolism, and its concentration is influenced by diet, malignancy, drugs, tissue hypoxia, metabolic acidosis and intoxication with alcohol or lead. It is moderately correlated with symptoms of severe CKD and is therefore usually used for evaluating ESRD. It may also be used to distinguish between prerenal and post-renal causes of uraemia. Cystatin C is produced in all nucleated cells and is less influenced by factors not related to renal function. Its use has been recommended in certain subpopulations, but

the assay is not standardized and has not been shown to be superior to either creatinine measurements when used as a screening tool in the general population (61) or creatinine-based eGFR calculations in subjects with a lower muscle mass (62). However, newer research has indicated that cystatin C might be a better predictor of progressive renal disease, since creatinine yields only limited information on this important issue (63).

Biomarkers in urine are measured for the earlier detection of renal injury or for prognostic assessments, and measurement of total urine protein using a dip-strip test has been a popular screening test for many years. The test strips usually react to albumin at concentrations greater than 150 mg/l, but they also react to other kinds of urinary proteins and may therefore yield limited information on pathological processes within the kidneys. More recently, urinary protein measurements have been replaced by more sensitive and quantitative tests that are specific for different proteins. For example, urinary albumin and immunoglobulin-G measurements are useful for detecting injury to the renal glomerulus, whilst elevated levels of alpha-1-microglobulin or beta-2-microglobulin indicate tubular damage (58).

While test strips may become less popular for identifying albuminuria, they are still used for detecting haematuria, such as that seen in urological cancer and glomerulonephritis. Microscopy analysis of urine is also useful in the latter condition for identifying specific blood cell casts, but further discussion of these methods is beyond the scope of this dissertation.

URINARY ALBUMIN

Methods and reporting procedures currently in use

The methods and procedures that are capable of accurately measuring low concentrations of urinary albumin (microalbuminuria) have been discussed for

decades (Table 2). Nephropathies are defined by the 24-hour excretion of albumin (or sometimes total proteins) in urine, but since this is a cumbersome and often inaccurate method, several surrogate measuring procedures exist. These methods include 4- to 12-hour urine collections and measurement of the urinary albumin excretion rate per minute. At present, the use of spot samples is common, with or without corrections for differences in urine concentration by measuring urine creatinine and calculating the ACR or protein:creatinine ratio. The ACR correlates acceptable with results from 24-hour collections (64) and is an often-favoured test (5, 6, 39, 45). Still, guidelines do not always give clear advice on the best procedure for measuring urinary albumin (54), and currently four different measuring procedures exist (Table 2: mg albumin/24 hours, µg albumin/min, mg albumin/l and mg albumin/mmol creatinine). The diagnostic cut-offs vary between countries (44, 45, 65-67), and a clear differentiation between albuminuria and proteinuria is sometimes lacking when this topic is discussed (65).

Table 2. Different procedures and cut-off values (range) for defining pathological urinary albumin (rows 1–3) or protein (row 4) concentrations (44, 45, 65-67).

	24-hour collection (mg/24 hours)	Timed collection (µg/minute)	ACR or protein:creatinine ratio (mg/mmol)	Albumin concentration (mg/l)
Normal	<30	<20	<2.0 to <3.4[a]	<20[b]
Microalbuminuria	30–299	20–199	2.0–3.4[a] (lower range) 19.9–33.9[a] (upper range)	≥20
Albuminuria	≥300	≥200	≥20 to ≥34[a]	
Proteinuria[c]	≥300 to ≥500[a]		≥30 to ≥50[a]	Positive dip strip

[a]Range of different cut-offs that are used
[b]A clear cut-off is not defined
[c]Measuring total urinary protein

Due to the large biological variation that occurs irrespective of the measurement procedure (54), current recommendations state that an elevated urinary albumin result should be confirmed within 1 week to 6 months, and at least two out

of three results should be above the diagnostic cut-off before microalbuminuria is diagnosed (44-47, 68). Albumin excretion varies during the day, and may be higher after physical activity. Morning samples are therefore recommended for analysing the ACR or albumin concentration. Point-of-care testing (POCT) instruments with good analytical quality are available (69, 70), and testing may therefore be performed both in hospital laboratories and the offices of general practitioners (GPs). Dip-strip tests that are sensitive to low concentrations of albumin are also used, but the results are more difficult to interpret since values are reportedly qualitative, and the analytical performance is variable.

Interpretation of urinary albumin results

Urinary albumin is elevated in up to 10% of the general population and is correlated with increased risks for CVD and ESRD (13, 71-73). To prevent the progression of renal disease, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) are recommended in all CKD and diabetic patients with albuminuria (40, 41, 44-47); blood pressure control based on ACR values is also suggested (6, 44-47). Diabetic patients with albuminuria should have intensified treatment of risk factors for macro- and microvascular disease; that is, increased use of statins and acetylsalicylic acid (ASA) and a lower Hba1c threshold than the often-suggested value of about 7% (44-47).

When urinary albumin results are used for monitoring the progression of renal disease it might be difficult to interpret when changes in serial results are of clinical significance. A recent review article evaluating 25 studies on biological variation found large variations in reported CVi values, both between and within the different methods. The lowest variation was seen for ACR measurements (54). Aggregating these data provides an estimate of the CVi and CD values that may be expected using different urinary albumin measurements (Table 3) (54).

Table 3. An overview of CVi values obtained in 25 different studies (54), listing the overall 25th, 50th and 75th percentiles for the CVi of different procedures and the corresponding CD value (two-sided test, 95% confidence interval, CVa of 5%). *n*=number of reported CVi values.

		CVi (%)			CD (%)		
	n	25th percentile	50th percentile	75th percentile	25th percentile	50th percentile	75th percentile
24-hour collection	16	21	36	49	85	142	193
Timed collections	20	32	41	56	127	162	220
ACR	34	25	34	50	100	135	197
Urinary albumin concentration	22	27	41	60	108	162	236

ESTIMATING THE GLOMERULAR FILTRATION RATE

Development of formulas for estimating glomerular filtration rate

In-vivo biomarkers for renal function such as creatinine and cystatin C are affected by factors other than GFR (74), and this may lead to delayed identification of renal disease in certain populations. Several formulas that have been developed to compensate for this are based on the correlation between the measured GFR and the average value of one or more biomarkers found in different subpopulations. The first formula used was that described by Cockcroft and Gault in 1976 (75), which included age, gender and body weight in the calculations. The Modification of Diet in Renal Disease (MDRD) formula was developed recently (76), based on age, gender and ethnicity. This formula shown an acceptable correlation with measured GFR values up to 60 ml/min/1.73 m^2 (77), is standardized to different creatinine assays (78) and is easy to report automatically since age and gender information can be obtained from the patient's social security number. This is currently the most frequently used formula for adult populations, but there are also several other formulas available both for adults and children (79-83).

Recommended use and interpretation of MDRD-based estimated glomerular filtration rate results

MDRD-based eGFR values are used for diagnosing (classification and staging) and monitoring renal disease. They are easy to obtain and more accurate than some of the more cumbersome methods (e.g. creatinine clearance) (84-86). This makes the screening of large populations possible, and it has been shown that reporting eGFR values facilitates the early diagnosis of renal disease (87-89) and can be used for drug dosing (90). The current recommendations are that eGFR values should be reported automatically with all creatinine results (3-6, 38).

eGFR reporting still has certain limitations. First, the label "eGFR" may mislead physicians into thinking that this is a more advanced GFR measurement than just an age- and gender-adjusted creatinine value. eGFR values have an overall negative bias of 6% relative to GFR measurements by renal clearance, and only about 80% of estimated values fall within ±30% of the measured GFR (77). This implies that for a measured GFR value of 50 ml/min/1.73 m^2, there is an 80% chance that the corresponding eGFR value would lie in the range 35–65 ml/min/1.73 m^2. Pre-analytical factors such as diurnal variations (91), ingestion of cooked meat (92, 93) and biological variation of creatinine (94) may explain some of the inaccuracy associated with eGFR results, but most of it is probably related to differences in muscle mass between subjects, which are only partly compensated for. The available guidelines do not usually emphasize the clinical situations in which eGFR results are regarded as being sufficiently accurate for clinical decision-making, and when measured GFR examinations are necessary (3, 5, 38).

Second, the formula used has not been validated for many populations (e.g. different ethnic groups, pregnant woman, critically ill patients and Fabry disease), and yet values are still reported automatically and may often be interpreted by clinicians as valid measures (95, 96).

Third, a common recommendation is that exact values should only be reported for CKD stages 3–5, since the formula does not provide sufficiently accurate values at higher levels, and such results are usually reported as >60 ml/min/1.73 m^2. Physicians may therefore take 60 ml/min/1.73 m^2 to be the lower limit of the reference range or the action limit for CKD, and further investigations including urinary albumin measurements might not be performed leading to delayed diagnosis of patients with CKD stage 1 or 2.

Many diabetes and CKD guidelines recommend annual eGFR monitoring (5, 6, 40, 41, 43) to identify progression in renal disease, but often give little information on the magnitude of differences that might be expected in subsequent eGFR results (2, 4, 5). One guideline suggests that a 6-month 15% decline in GFR is clinically significant (3), whilst others suggest that a 1-year decrease of 4 ml/min/1.73 m^2 is rapid (2), and yet others emphasize that a CVi of 5% should be expected for creatinine values, but do not suggest the degree of change that can be anticipated for consecutive eGFR measurements (6). Guidelines recommend that patients with CKD stage 4 or 5 should be referred to nephrology care (3, 6), but for stage 3 patients the advice varies, from a 1-year decline of 5 ml/min/1.73 m^2 (6) to a 6-month 50% decrease (3) in eGFR values.

COMMUNICATION BETWEEN LABORATORIES AND CLINICIANS

Laboratories communicate with clinicians through the test repertoire they offer, the lay out of request forms (97, 98), reporting of commented or uncommented test results (87, 99, 100), occasional personal contact with physicians, laboratory newsletters and educational programmes arranged by the laboratory (88, 101). Specialists in laboratory medicine working in clinical chemistry laboratories are involved in the implementation of new test procedures and may, according to the

International Standard for Accreditation of Medical Laboratories (ISO 15189), be expected to advise clinicians on the interpretation of test results. Interpretive commenting of new or complicated tests can be valuable (87, 102) and is greatly appreciated by physicians (103). The information provided to clinicians from the laboratory is usually based on the laboratory professionals' experience with analytical procedures and the literature, including textbooks, scientific articles and guidelines.

Some challenges related to this practice should be acknowledged. First, there is general a large amount of scientific literature related to the use of different kinds of laboratory analyses and interpretation of results, and this information is sometimes conflicting. Furthermore, low-quality information may be prominent (e.g. opinion papers, consensus statements and non-peer-reviewed papers), and if these publications are not in agreement with scientific findings they might lead to suboptimal practice. The scientific literature for other topics, such as request forms and algorithms for reporting of results, may be scarce. Several articles have shown that the quality of guidelines might be low (104-106) and that many recommendations are based on consensus or low-quality evidence (107). As a consequence, the laboratory professional may focus on different aspects, reach different conclusions and give different advice, which is highly likely to lead to diverse and sometimes low-quality laboratory practices (108-110). Studies have shown that the commenting of laboratory results by laboratory professionals may also be of variable quality (111-113), even for common laboratory tests including renal parameters (114). It may be anticipated that the laboratories performance related to these issues may have impact of follow-up and treatment of patients.

AIMS OF THE STUDY

The main aim of this work was to elucidate the use and interpretation of urinary albumin and eGFR in primary health care and relevant advices offered by laboratory specialists. We also aimed to uncover some of the consequences of misinterpretation of such test results. The detailed aims of this study were as follows:

- To determine the use and interpretation of urinary albumin testing in primary health-care in different regions of Europe, with emphasis on the availability of equipment in the physician's office and what changes in urinary albumin results GPs considered clinically important (Article I).

- To compare GPs' knowledge of urinary albumin testing with guideline recommendations in patients with type 2 diabetes, and how the presence or absence of microalbuminuria influences drug treatment (Article II).

- To examine how CKD stage 3 patients are investigated and treated in primary health care, with special emphasis on the use of creatinine, eGFR and urinary albumin, and what changes in creatinine and eGFR results that were considered clinically important by GPs (Article III).

- To explore what advice laboratory specialists would give to clinicians, focusing on three aspects: (i) what further testing should be recommended in primary health care for a diabetic or hypertensive patient after obtaining laboratory results suggesting possible renal damage, (ii) what changes in eGFR and ACR results should be considered clinically significant, and (iii) the extent to which laboratory specialists anticipate uncertainty of MDRD-based eGFR results (Article IV).

SUMMARY OF ARTICLES

ARTICLES I AND II – ANALYTICAL AND CLINICAL ASPECTS OF URINARY ALBUMIN MEASUREMENTS IN PRIMARY HEALTH CARE

Subjects and methods

A case-history-based questionnaire was posted to approximately 10,000 GPs in 10 European countries and Australia. Since urinary albumin examination is probably most established for diabetic patients, a case history was formulated based on the profile of a male type 2 diabetic patient in whom urinary albumin testing had not been performed (see Appendix 1), and questions were posed related to diagnosing microalbuminuria, and follow-up and treatment of the patient. Clinically important changes in urinary albumin results were evaluated. Assuming long-term random bias (e.g. due to calibrations of different reagent lots to be included in the CVa), the anticipated CVa was calculated for the ACR using a CVi of 24% (year-to-year variation) (115) and *z* values of 1.64 and 0.84 reflecting confidences of 95% and 80% (one-sided test), respectively. A four-page feedback report was translated into the native languages of the recipients and sent to all participants including an update on the laboratory and clinical implications of microalbuminuria (see Appendix 2).

Results: Article I

In total, 2078 GPs from 9 countries were included in the study described in Article I, and the response rate varied from 7% to 43% depending on the country, with the availability of in-office testing ranging from 4% to 88%. For a first-time examination for microalbuminuria, GPs in most countries preferred to use morning or random

urine samples rather than timed collections. Overall, 62% of GPs stated that they would repeat the testing in order to confirm a positive result. Differences in the use of test materials were related to in-office equipment: for first-time examination, 95% of GPs with in-office testing and 70% of GPs without in-office testing used morning or random urine samples, while for repeat tests 63% of semi-quantitative strip users, 31% of quantitative albumin measurement users and 16% of ACR users preferred a repeat test to be done in a larger laboratory. When such a laboratory was used for follow-up tests, the use of timed samples was high, and similar between GPs with or without in-office testing (64% vs 57%). In all but one country, all four measurement units were used when CDs were stated. The median CDs for the estimation of a clinically significant increase or decrease in urinary albumin were similar in most countries (30–35%). CD did not vary with the unit category that was reported. The median CVa values required to meet the clinical CD requirements with 80% confidence were similar (at about 14%) in most countries for both an increase and decrease in ACR values.

Results: Article II

Almost all of the GPs who responded in the study described in Article II would request urinary albumin for diabetic patients, whereas fewer would use it to evaluate patients with hypertension or renal disease. The availability of in-office methods for urinary albumin seemed to broaden the indications for the test. Negative and positive test results appeared to be followed up with a new test after 6–12 and 1–3 months, respectively. Drug treatment would be supplemented by 61–91% of GPs in the various countries if the patient was normoalbuminuric, and nearly 100% would do so if the patient had microalbuminuria, mainly by adding statins and ACEIs or ARBs. The proportion of GPs recommending all four treatment alternatives [grouped as ASA, blood glucose-lowering agents (insulin and oral hypoglycaemic agents), antihypertensives and statins] was low, but increased by 8–12% when the patient had microalbuminuria.

ARTICLE III – INVESTIGATION OF CHROINC KIDNEY DISEASE STAGE 3 IN PRIMARY HEALTH-CARE

Subjects and methods

The patients and GPs were selected by searching laboratory databases for creatinine results obtained in 2008 at the two university hospitals in the Norwegian cities of Bergen and Stavanger. The search criteria were primary-care patients between 40 and 70 years of age who had two eGFR results requested by the same GP (more than 3 months apart) that did not differ by more than 5 ml/min/1.73 m^2 and ranged between 30 and 59 ml/min/1.73 m^2 (corresponding to CKD stage 3). 386 physicians had received creatinine and eGFR results for a patient who fulfilled the inclusion criterias. To these GPs were sent a questionnaire collecting information on their assessment of the patient (the youngest patient was chosen if a physician had multiple patients). The questionnaire evaluated the abilities of the GP to categorize the patient's renal function and what changes in creatinine and eGFR were considered clinically important or would lead to referral of the patient to nephrology or internal medicine care. Furthermore, we explored what examinations had been carried out, relevant co-morbidity diagnosed and drug treatment of the patient. The questionnaire was pilot-tested by ten GPs. The study was designed in accordance with the guidelines of the Regional Committees for Medical and Health Research Ethics and the Norwegian Privacy Ombudsman for Research, and the patients and GPs were anonymous to the researchers. The theoretical CD for creatinine was calculated to be 13%, assuming no systematic change between the two measurements, a *z* value of 1.64 (95% confidence, one-sided test), a CVa of 2% (CVa from routine creatinine measurements at the two hospitals in Bergen and Stavanger) and a CVi of 5.3% (94). Using the CD for creatinine (±13%) in the MDRD formula (116), the calculated CDs for the eGFR results were 13% for impaired and 17% for improved renal function.

Results: Article III

The response rate in the study described in Article III was 60%; 19 respondents were excluded since they were not the GP usually caring for the patient, leaving 210 GPs to be included. The median age of the patients was 63 years, 53% were females, and 73% had some kind of co-morbidity [hypertension (60%), CVD (25%) or diabetes (20%)]. Creatinine values were 124 µmol/l for the males vs 95 µmol/l for the females, whilst eGFR values were similar for the two genders: 52 vs 51 ml/min/1.73 m^2. Overall, two-thirds of patients had a urine dip strip and/or a urinary albumin measurement. In total, 20% had two positive tests for urinary albumin (12%) and/or urine dip strip (13%), and this was defined as albuminuria. Of the 53 dip-strip-negative patients, approximately half had a urinary albumin measurement, and 10 (19%) were diagnosed with albuminuria. Of the 42 patients who were diagnosed with albuminuria, 95% had CVD, hypertension or diabetes, and 79% used ACEIs or ARBs. Even though all patients had CKD stage 3, only 27% (55/201 patients) were categorized by GPs as having moderately reduced renal function (stage 3); the classification was more likely to be correct in males. Median changes to signal improvement or deterioration in renal function, or to indicate referral were 14 (12%), 20 (18%) and 40 (36%) µmol/l, respectively, for creatinine, and 8 (17%), 8 (17%) and 13 (26%) ml/min/1.73 m^2 for eGFR. Albuminuria did not influence the classification or magnitude of the clinically meaningful changes stated.

ARTICLE IV – INTERPRETATION OF ALBUMIN:CREATININ RATIO AND ESTIMATED GLOMERULAR FILTRATION RATE RESULTS BY LABORATORY PROFESSIONALS

Subjects and methods

A questionnaire was developed containing three case histories that mimicked a situation where a clinician contacted the laboratory to discuss renal parameter results in these patients. Case 1 depicted a male primary-care patient with hypertension, a creatinine value of 119 µmol/l (reference range 60–105 µmol/l) and an eGFR of 54 ml/min/1.73 m^2, corresponding to CKD stage 3. The second case described a male primary-care patient with diabetes and an ACR result of 15 mg/mmol. The descriptions of the case histories were followed by questions regarding further investigations and the changes in serial results that would be considered to be clinically significant. The third case history represented a typical hospital situation: a 57-year-old female patient with borderline reduced renal function who should commence a nephrotoxic chemotherapy treatment regime. Questions were posed regarding how her renal function should be monitored before and during treatment.

The questionnaire and reminders were distributed in 2009 by mail to 76 physicians working in Norwegian laboratories. In the Netherlands, the questionnaire was sent to 24 laboratory specialists as part of a regular external quality assurance programme that covers the interpretation of laboratory results. Tests suggested by the laboratory specialists were based on recommendations in international guidelines (5, 6, 38-42), classified by the authors as either "useful" or "unnecessary", and the number of laboratory specialists who suggested (based on the same guidelines) an "optimal test panel" for the primary-care patients was noted. For patient 1, the "optimal test panel" included repeating eGFR measurement and testing for albuminuria (urine dip-strip and/or urinary albumin or protein measurements). Screening for haematuria (dip-strip or sediment) was regarded as appropriate but not

a requirement. For patient 2, repeated urinary albumin testing and eGFR measurement were regarded an “optimal test panel”, whilst for patient 3, gold-standard clearance testing (e.g. iohexol, iothalamate and Cr-EDTA clearances, but not creatinine clearance) (6), eGFR and testing for albuminuria (urine dip-strip and/or urinary albumin or protein measurements) were found to be useful.

Results: Article IV

The response rate in the study described in Article IV was 52%, and 52 participants were included. Less than 30% of respondents suggested performing an optimal test panel for the primary-care patients in cases 1 and 2. Based on the first case history, 52% recommended retesting of eGFR and 69% advised a follow-up urinary albumin test in a diabetic patient with an elevated ACR. For creatinine and eGFR, the median changes considered to represent improvement or deterioration in renal function were similar to what could be calculated using CVi values from the literature (creatinine, 14% and 14%, respectively; eGFR, 18% and 13%, respectively), whilst for the ACR (50% and 67%, respectively) the values were variable and lower than the calculated ones. In case 3, 23% would recommend an accurate clearance measurement to be performed before the patient started the nephrotoxic chemotherapy regime, and 8% would recommend this before every chemotherapy cycle. For all case histories, approximately 20% of suggested tests were regarded as unnecessary.

DISCUSSION OF THE METHODS USED

Questionnaire-based research may be complicated by different biases, and the following section includes a discussion of the methods used and their validity. The first part evaluates internal validity, including a general discussion on how questionnaires may be used as research tools. This is followed by comments on how the questionnaires were designed, recruitment of participants, registration of responses to assure good-quality data (117) and the statistical analyses chosen. The second part assesses the external validity of our findings.

INTERNAL VALIDITY

The use of case histories and chart abstractions as research tools

In this work we used questionnaires including one or up to several case histories (Articles I, II and IV) and a questionnaire for which data were extracted from patient files (Article III). There is currently debate regarding how to obtain reliable information on physician's actions and knowledge. Direct observation is usually considered to be the gold-standard method, but this is often not feasible due to it being cumbersome, time-consuming and expensive. The presence of an observer, tape recorder or camera in the physician's office may also bias the physician's or patient's actions. The use of patient vignettes or chart abstractions may be used as a substitute for direct observations, and several studies (including two reviews; (118, 119) have evaluated the accuracy of these methods. It has been suggested that the use of case-history-based questionnaires leads to overreporting of actions compared to other approaches (118-120). However, patient vignettes are still regarded as an efficient and robust way of measuring a GP's knowledge because measurements are standardized (i.e. all GPs have the same information) (121). In some newer studies, GPs were consulted by standardized patients whom they believed were real patients

(gold standard), and actions taken during the consultation were compared to chart abstractions (from the same consultation) and responses to a similar case history presented in a questionnaire. Vignettes were found to be a better tool for evaluating GPs' actions than were chart abstractions (122-124), and were especially suited for evaluating variations in practice between different sites (122, 123).

Patient files include most of the GPs' actions and assessments in different situations, but may not reflect their actual knowledge. Data abstracted from patient files are influenced by the great heterogeneity that may be seen between patients (e.g. resulting from differences in compliance, patient preferences and co-morbidities). Studies using different gold standards (e.g. standardized patients, trained observers or audio/video recording) have shown varying specificities (range 81–100%) and sensitivity (range 60–83%) for evaluating the follow-up and treatment of patients based on data from journal files, and in particular actions might be underreported (118, 125). However, a higher degree of validity was seen for the reporting of specific clinical actions, as done in Article III (118).

Designing the questionnaires

The case histories and questionnaires were carefully designed after exploring the literature of specialists in primary health care and clinical chemistry with long-term experience in designing questionnaires used among primary health-care physicians (126-136). For Articles I, II and IV, real patients were used as models for the case histories, whilst for Article III the questionnaire obtained data of one of the patients enlisted with a GP. The questionnaires were simple to complete, had a closed format to facilitate similar interpretation of the questions between GPs and included space for open-format comments. All questionnaires were peer reviewed by other researchers, and those used for Articles I–III were pilot-tested by GPs.

Recruitment of study subjects and data registration

The focus of the first survey (Articles I and II) was to elucidate the potential problems related to urinary albumin testing and to collect data from geographical areas with diverse medical traditions and organization of health care, in order to make the observations more robust and possibly highlight differences in the correct use and interpretation of the test. The inclusion of GPs was not related to the specific topic studied (urinary albumin testing), but rather to other factors (e.g. geographical location, laboratories used and participation in external quality assessment schemes). For Article III, the hospital laboratory databases were searched for eligible patients using defined inclusion criteria, and all identified patients were included (except in a few cases where GPs had more than one patient fulfilling the inclusion criteria, in which cases only the youngest patient was included). For Article IV, all registered Norwegian laboratory specialists as well as doctors specializing in clinical chemistry were eligible for the survey. Retired professionals or those known by the authors to work in other specialties were excluded. In the Netherlands, most clinical chemists have a scientific background and only a minority have medical training. The questionnaire was sent to 24 laboratory specialists as part of a regular external quality assurance programme that covers the interpretation of laboratory results.

In the first survey (Articles I and II), responses were registered by national collaborators into a custom-made Web-based application, accessible only with country-specific usernames and passwords. A detailed instruction manual including information on how responses should be interpreted was provided to assure that the data registration was similar in all countries. For Articles III and IV, all replies were registered by one person (K.M.A.), thereby assuring a similar interpretation of the responses.

Response rate

The response rate was low for all of the surveys. This was expected for several reasons, not least because physicians often exhibit low survey response rates (126-128, 137, 138). First, for Articles I and II it was necessary to use a somewhat longer questionnaire compared to what had been used previously by our group (127-129, 131) due to the complexity of the issue. Second, studies have shown that less than 30% of GPs follow the recommendation of annual screening for urinary albumin (138-142), indicating that this is an unfamiliar subject to most GPs. A higher response rate was seen for Article III (60%), probably due to the use of real patients and exploring the use of a well-known test (creatinine). The lower response rate obtained for Article IV may reflect that many laboratory specialists do not work primarily with renal parameters. In all of the surveys, the questions on CD had the lowest response rate (70–80% of responders; for Article IV this was only seen for the question related to the ACR). This question was simplified after pilot testing (Articles I and II), and similar wording was used in the subsequent questionnaires. The most-likely reason for the low response rate is that physicians find these questions difficult to answer.

The relatively low response rate could have influenced the results. The characteristics of the participating Norwegian GPs (i.e. their age, gender, specialization in primary health care and working in group practice) were similar to those of Norwegian GPs in general (personal communication; Andres Taraldset, The Norwegian Medical Association), and it is unlikely that non-responders are more skilful or have more knowledge about laboratory and clinical issues related to renal disease compared to the responders. Thus, if a higher response rate had been obtained, a larger variation within the results may have been expected; our findings should therefore be interpreted as “best practice” data.

Statistical analyses

For all articles robust and well-known statistical analysis techniques (Student's *t*-test and chi-square test) were used to evaluate differences between relevant groups in continuous or categorical variables. McNemar's test was used to evaluate differences between proportions in paired samples (Article II). Multiple logistic or linear regression was determined to be applicable to exclude possible confounding effects exerted by the different dependent variables on the outcomes measured. Statistical analyses were performed using SPSS versions 14.0 to 18.0, and the level of statistical significance level was set at $p<0.05$.

EXTERNAL VALIDITY

The data presented in Articles I and II were obtained from different areas of Europe. It seems reasonable to assume that urinary albumin testing would be used less in health-care systems with less resources, and therefore our data might not be applicable to developing countries. The data in Article III were collected in two areas of Norway; whether these findings are representative of other countries remains to be determined. However, this study was designed to evaluate GPs' actions related to renal disease when measurement of the eGFR had been implemented without a special educational programme or comments regarding the results from laboratory specialists. Changes in the laboratory protocol or reporting algorithms are usually implemented this way, and our findings may therefore be generalized to similar situations. The last article included laboratory specialists from two European countries. No statistical differences were found between the data obtained in Norway and the Netherlands; similar findings regarding the evaluation of laboratory specialists' interpretation of laboratory results have also been shown by others (111-114). These results are thus likely to be valid for other regions, at least in developed countries.

DISCUSSION OF THE RESULTS

This section focuses on how knowledge related to urinary albumin and eGFR may affect a physician's actions, and how misinterpretation of the test results may affect the utility of laboratory analysis results. The last part of the section focuses on informational strategies related to the implementation of new laboratory test procedures.

Changing the indications or procedure for an established laboratory test

An obstacle to optimal test utilization demonstrated by our findings was a lack of knowledge related to renal parameters amongst both laboratory staff and GPs. The data from primary health-care showed that albuminuria testing was more common in diabetic than in (for example) hypertensive or CKD patients (Articles II and III), and that relatively few laboratory specialists would recommend albuminuria testing in a hypertensive patient suspected of having CKD (Article IV). This is probably due to this laboratory procedure having been recommended for decades in diabetic patients, whilst its use is fairly new for hypertensive or CKD patients (32, 143, 144). A relatively low percentage of both GPs (62%) and laboratory specialists (69%; Articles I and IV) would suggest that a positive urinary albumin result is confirmed, as recommended by guidelines due to the large biological variation for this constituent. This could result in both false-positive and false-negative albuminuria diagnoses.

Articles I and IV demonstrate that many hospital laboratories perform or recommend suboptimal laboratory procedures for the assessment of urinary albumin, and Article III indicates that insensitive urine protein tests are often used in primary health care. Changes in the recommended procedure for performing a well-known analysis (i.e. from measuring urinary albumin after 24-hour urine collections to measuring the ACR in a morning sample) may be impeded for various reasons. First, guidelines might not be updated. In France, 80% of GPs would use 24-hour

collections for albuminuria testing (Article I), which is not necessary but can probably be explained by the local guidelines still recommending this (145).

Second, even if the optimal procedure is recommended on a national basis, local laboratories may not offer it, or else GPs may use POCT instruments that are not capable of performing the new procedure. Article I describes how GPs in France and Spain (mostly using hospital laboratories) were accustomed to albumin results reported as mg/24 hours reflecting that timed collections were offered by the laboratories. This assumption is strengthened by the finding that GPs who performed confirmatory testing in hospital laboratories used timed collections, as opposed to those GPs performing confirmatory testing in the office laboratory preferring the ACR. The use of the ACR was highest in Scandinavia. In Norway and Sweden, POCT instruments were common, and approximately two-thirds of those reporting the type of in-office instrument used had an ACR instrument (Article I). In Denmark, in-office testing is not common, but a high frequency of ACR use was still recorded. Both approaches (in-office or hospital testing) may therefore be adequate, depending on the availability of the optimal test procedure.

The use of different practices in different countries indicates that changing the indications or test procedure after a test is implemented is a difficult and slow process. After auditing the current practice, we sent a feedback report to all participants that showed their results and gave an update on the use and interpretation of urinary albumin results. The aim of this was to increase GPs' knowledge regarding the subject and its effect may be evaluated in a later study. Actions should be taken by the relevant medical societies to inform users of laboratory analyses or laboratories about current evidence-based recommendations. Another strategy that has been proven to increase the use of routine laboratory tests (e.g. urinary albumin) is increased reimbursement for performing the most relevant test procedure (146). This decision is in the hands of health-care authorities, but could also be promoted by the medical and laboratory societies.

Information strategy for implementing new reporting algorithms for laboratory tests

The reporting of eGFR results is recommended to facilitate an earlier diagnosis of CKD, and is assumed to be especially useful in populations with lower muscle mass (e.g. women and the elderly) who might have creatinine results within the normal range even if reduced renal function has developed. Article III shows that CKD was identified less in subjects with normal or only slightly elevated creatinine values (i.e. women), indicating that the continued reporting of creatinine with eGFR results in CKD stage 3 might be counterproductive with regard to facilitating an early diagnosis of CKD (147). An information newsletter was provided by the laboratories when eGFR reporting was implemented, as is usual when Norwegian hospital laboratories change procedures or protocol, and an article explaining the interpretation of eGFR results was published in the Journal of the Norwegian Medical Association (148). It was clearly demonstrated that this was not sufficient to inform GPs, and so more substantial educational efforts seem necessary (88, 101, 149).

A simple way of communicating the meaning of laboratory results to GPs could be to produce interpretive comments that are automatically reported along with the test result. Such an approach has been attempted for eGFR, and has led to a substantial increase in the rates of referral of CKD patients (87). In this way laboratories could act as an informational channel to GPs, thus efficiently facilitating an increased referral or use of routine urinary albumin testing in CKD patients. However, as demonstrated by the study described in Article IV and by earlier studies (111-114), laboratory professionals may offer misleading advice regarding the interpretation of common laboratory tests, and probably need guidance about performing such a task. Before a commenting procedure is implemented, it should be discussed within the relevant professional societies (which for eGFR would at least include clinical chemists and nephrologists), and any comments or reporting algorithms suggested would benefit from being pilot-tested.

Such preparations prior to recommending a change may seem extensive, but all of the articles included in this dissertation indicate that changing established laboratory procedures or establishing new ones is a slow and difficult process. As a consequence, guidelines and position statements recommending new test procedures or reporting algorithms for laboratory tests would benefit from including clear and detailed strategies that facilitate the implementation of these changes.

Consequences of misinterpretation related to urinary albumin testing

More information on mortality and the progression of renal disease could usually be obtained from the presence of albuminuria than from the eGFR value itself (11-13), and urinary albumin investigations are recommended in all diabetic or CKD patients (5, 6, 39-41). All CKD or diabetic patients with albuminuria should be treated with ACEIs or ARBs (5, 6, 40, 41, 150), and Article II describes that a diagnosis of albuminuria results in GPs intensifying the treatment of a diabetic patient. It is therefore possible that the insufficient use of urinary albumin investigations in a substantial number of CKD patients or patients at risk of CKD that was demonstrated in Articles II and III could lead to inadequate treatment and an increased risk of complications.

Chronic kidney disease staging and applicability in clinical practice

The data presented in Article III show that most of the GPs did not interpret eGFR results according to the CKD classification system. However, that staging system has been criticized for not reflecting the clinical course of renal disease (8) since albuminuria, which is a more powerful prognostic predictor of the progression of renal damage (9, 11-13), is not included. Most GPs probably categorize renal disease according to their clinical experience, and since only 20% of patients included for Article III had albuminuria, GPs may have experienced that most of these patients

have a relatively stable renal function. This could explain why they did not find it appropriate to use the term "moderately reduced" to describe the patients' renal function. An update of the CKD system to include albuminuria (8, 15, 16), thereby improving its agreement with the clinical course of renal disease and clinical experience, is supported by our findings.

Interpretation of consecutive test results

One of the main focus in this work was to ascertain the magnitude of changes in test results that GPs considered necessary to signal an important change in the patient's clinical condition. There were large discrepancies between GPs, and many physicians denoted higher values than the CD calculated using the method suggested by Fraser and Harris (55). The great heterogeneity and the lower response rate to these questions show that the GPs had very diverse experiences, and that it is difficult to suggest such values, even for well-known patients. One reason is that the confidence intervals that GPs use when interpreting changes in test results (e.g. 80% or 99%) may differ from the 95% confidence intervals often used when calculating CD values. If more than two results are included in the series of test results evaluated (common in primary health care), this should (at a given level of confidence) lead to action as a result of smaller changes compared to if only two results are evaluated. A large variance in responses was seen when clinical chemists (who are accustomed to calculating CD) were asked to denote important changes in the ACR compared to creatinine and eGFR values. Our findings reflect that the information on CD is either limited or heterogeneous in the scientific literature (as for the ACR), or that the concept may be unknown to the respondents (especially in primary health care), since it is not communicated in guidelines or Web-based information tools.

One important limitation of the concept of CD is highlighted by our findings. The clinically important changes reported by GPs are probably not based on calculations or statistics, but rather on their clinical experience; that is, the outcomes of earlier patients who experienced similar changes in serial values. The CD is

defined as the minimum difference needed between two consecutive results to be certain (with a specified level of confidence) that the results are truly different, and that the difference is not due only to analytical variation and biological (CVa and CVi). Even so, in clinical practice, not all changes exceeding the calculated CD values are important because only changes that are associated with an adverse or improved outcome (as defined by clinical outcome studies) are important. Clinically significant changes may therefore occur both outside and within the limits of the calculated CD, depending on the constituent measured and the disease monitored. The probability for the change to represent an important change in the patient's situation (i.e. improved or adverse outcome) may be calculated in a model including differences between two consecutive test results, prevalence of the disease (or prevalence of an improvement in the condition) monitored, and analytical variation of the constituent measured (56). This information could be useful when clinicians are interpreting repeat test results, and the consequences of making such information available to clinicians should be explored in future research studies.

Setting analytical goals based on clinicians' anticipation of significant clinical changes

Using the CDs stated by doctors, it is possible to calculate the minimum analytical imprecision (assuming a zero bias between consecutive test results) anticipated by GPs, and compare this to what it is actually possible to achieve using POCT or hospital instruments. This was done in Article I because GPs conducted urinary albumin measurements in their office, and therefore the analytical quality of the instruments is important. We found that in most cases the GPs' expectations were in line with what could be obtained if an 80% CI was used, and this is probably sufficient for clinical practice.

MAIN CONCLUSIONS

Our data suggest that the following features related to albumin and the eGFR have not been acknowledged by or conveyed to GPs:

- Guidelines on diagnosing microalbuminuria are only partially followed. Timed collections or spot samples measuring urinary albumin concentration still dominate in some areas. Repeat testing after obtaining a positive result is conducted by one-half to two-thirds of physicians, and anticipated CD values are lower than those calculated based on CVa and CVi.

- The medical treatment of diabetic patients after a diagnosis of microalbuminuria is currently insufficient when compared to guideline recommendations.

- CKD stage 3 patients are insufficiently examined for albuminuria and appear to be referred to hospital care after larger eGFR declines than are recommended by the guidelines.

- ACR and eGFR values from diabetic or hypertensive patients are interpreted differently by laboratory specialists, and this could result in different advice being offered to clinicians, which again may adversely affect patient care.

As revealed by our data the reasons behind the insufficient use and interpretation of urinary albumin and eGFR results may be the conflicting or suboptimal recommendations provided by guidelines, inadequate educational efforts when implementing new or changing established test procedures, incongruence between GPs' clinical experience and the recommendations, and limited research data on some issues. This may ultimately reduce the quality of health care provided to primary-care CKD patients.

FUTURE PERSPECTIVES

The following further work would be useful to improve the quality of laboratory-related recommendations and communications:

- Evaluating whether the feedback report (including an update on the use and interpretation of urinary albumin) that was sent to all respondents for Articles I and II has improved GPs' knowledge related to the use and interpretation of urinary albumin results.
- Examining the way in which commenting of eGFR results may affect the follow-up and treatment of primary health-care CKD patients.
- Determining how recommendations from international clinical chemistry societies may be better conveyed to laboratory specialists working in local clinical chemistry laboratories.
- Exploring how to improve the communication between laboratory specialists and clinicians.
- Developing a database including clinically significant changes for common laboratory tests that combines information from clinical outcome studies (e.g. studies providing information on the magnitude of changes signalling adverse or improved outcomes) and CD (changes that might be seen in a stable situation) should be established, and its subsequent effects on clinical practice should be evaluated.
- Generating a checklist stating what information should be included on laboratory analyses in clinical guidelines. Examples of such information could be what specimens are suitable to use, important pre-analytical conditions, major analytical interference, biological variations, clinically important changes in consecutive results, the need for follow-up testing after obtaining a positive result and strategies for the implementation of new test algorithms.

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