Editor's key points

- With more than 3 million Canadians currently diagnosed with diabetes and with a urine albumin-to-creatinine ratio (ACR) test costing about $11, a simpler diagnostic model for chronic kidney disease (CKD) in diabetes might be economically advantageous.
- In this study there was a strong positive predictive value for the first abnormal urine ACR (between 2 and 20 mg/mmol) to diagnose CKD at 96.80%. An evaluation of the relationship between the first and second urine ACR results (irrespective of whether a third test result was available) to derive a predictive probability plot revealed that there was greater probability of the second urine ACR being abnormal (≥2 mg/mmol) when the first urine ACR was greater than 6 mg/mmol.
- Several random urine ACR tests might not be necessary to diagnose patients with type 2 diabetes as having persistent microalbuminuria and CKD. Having multiple steps in the diagnostic pathway can negatively affect early detection and screening of diabetic nephropathy in primary care.

Chronic kidney disease in type 2 diabetes

Does an abnormal urine albumin-to-creatinine ratio need to be retested?

Divya Garg MD CCFP Christopher Naugler MSc MD FCFP FRCPC
Vishal Bhella MD CCFP Fahmida Yeasmin MSc

Abstract

Objective To determine the positive predictive value (PPV) of a single random abnormal urine albumin-to-creatinine ratio (ACR) compared with repeat test results in patients with type 2 diabetes to diagnose chronic kidney disease (CKD).

Design Retrospective, longitudinal secondary data analysis using Calgary Laboratory Services data.

Setting Calgary, Alta.

Participants Patients aged 21 and older with a new diagnosis of diabetes in the study period from January 2008 to December 2015 and with a first abnormal urine ACR followed by another ACR test completed within 120 days.

Main outcome measures The PPV of an abnormal urine ACR (2 to 20 mg/mmol) to diagnose CKD was calculated. A test result was considered a true positive if a subsequent positive test result (≥2 mg/mmol) was identified within 120 days of the first positive test result and a false positive if 2 subsequent negative test results were identified within the same time period. The relationship between the first and second urine ACR values to assess the probability of the second urine ACR being abnormal (≥2 mg/mmol) based on the values of the first abnormal urine ACR was also explored.

Results The PPV of the first abnormal urine ACR between 2 and 20 mg/mmol to diagnose CKD was calculated at 96.80% (95% CI 95.37% to 98.21%). Additionally, there was increased predictive probability of the second urine ACR being abnormal at higher values of the first urine ACR (2 to 20 mg/mmol). The data were further analyzed to exclude test results with a new or changed prescription of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker medications around the time of the first urine ACR test to focus results on screening and not treatment response. With these exclusions, the PPV for first urine ACR between 2 and 20 mg/mmol to diagnose CKD was calculated as 96.23% (95% CI 94.13% to 98.32%).

Conclusion The first random abnormal urine ACR has a good PPV for the diagnosis of CKD in patients with type 2 diabetes, so multiple random urine ACR tests might not be necessary to diagnose patients with type 2 diabetes as having persistent microalbuminuria and CKD. A simpler diagnostic model for diagnosing renal disease might improve patient compliance, efficiency of testing, and implementation of health interventions. Reduced testing would also be expected to result in reduced cost from a health care expenditure perspective.

Diabète de type 2 et maladie rénale chronique

En présence d'un rapport albumine/créatinine urinaire anormal, est-il nécessaire de répéter cet examen?

Divya Garg MD CCFP Christopher Naugler MSc MD FCFP FRCPC
Vishal Bhella MD CCFP Fahmida Yeasmin MSc

Résumé

Objectif Déterminer la valeur prédictive positive (VPP) d'une mesure unique et effectuée sur un échantillon pris au hasard du rapport albumine/créatinine urinaire pour diagnostiquer une maladie rénale chronique (MRC) chez des diabétiques de type 2 par rapport à la valeur de mesures répétées de ce paramètre.

Type d'étude Une analyse rétrospective longitudinale utilisant des données du *Calgary Laboratory Service*, en Alberta.

Contexte Calgary, en Alberta.

Participants Des patients d'au moins 21 ans avec un diabète nouvellement diagnostiqué durant la période de l'étude, entre janvier 2008 et décembre 2015, et qui avaient eu un premier résultat anormal de RAC suivi, dans les 120 jours suivants, d'un autre examen du même paramètre.

Principaux paramètres à l'étude On a calculé la VPP d'un RAC urinaire anormal (2 à 20 mg/mmol) pour diagnostiquer une MRC. On a considéré qu'un résultat d'examen était un vrai positif si on avait obtenu un autre résultat positif (≥ 2 mg/mmol) moins de 120 jours après le premier examen positif et qu'il s'agissait d'un faux positif si 2 examens s'étaient avérés négatifs au cours de la même période. On a également vérifié le rapport entre les valeurs du premier et du deuxième RAC urinaire pour déterminer la probabilité que le deuxième résultat soit anormal (≥ 2 mg/mmol) par rapport à la valeur du premier résultat.

Résultats On a calculé que la VPP d'avoir une MRC quand le premier résultat du RAC urinaire est anormal (entre 2 et 20 mg/mmol) est de 96,80 % (IC à 95 % 95,37 à 98,21 %). De plus, la probabilité prédictive d'avoir un deuxième RAC anormal était accrue quand le résultat du premier examen était plus élevé (entre 2 et 20 mg/mmol). Une analyse additionnelle des données a été faite en excluant les résultats associés à une nouvelle prescription d'un inhibiteur de l'enzyme de conversion de l'angiotensine ou à un changement de dose, ou à un traitement avec un bloqueur des récepteurs de l'angiotensine II à la suite du premier examen, afin de s'en tenir à l'aspect dépistage et non à une réponse à un traitement. Avec ces exclusions, la VPP d'un premier résultat entre 2 et 20 mg/mmol est de 96,23 % (IC à 95 % 94,13 % à 98,32 %).

Conclusion La première mesure anormale du RAC urinaire possède une bonne VPP pour diagnostiquer une MRC chez un diabétique de type 2, de sorte qu'il pourrait être inutile de prendre plusieurs mesures additionnelles de ce paramètre pour diagnostiquer une microalbuminurie persistante et une MRC. Avec une façon plus simple de diagnostiquer une maladie rénale, on pourrait améliorer la compliance du patient et l'efficacité de l'examen, et permettre une intervention plus précoce. On peut également s'attendre à ce qu'une diminution de ce type d'examen entraîne une réduction des coûts pour le système de santé.

Points de repère du rédacteur

- Puisqu'il y a plus de 3 millions de diabétiques au Canada et que la mesure du rapport albumine/créatinine (RAC) dans l'urine coûte environ 11 $, il pourrait être économiquement avantageux d'utiliser un moyen plus simple pour établir un diagnostic de maladie rénale chronique (MRC) chez un diabétique.
- Cette étude a révélé qu'une première mesure du RAC (entre 2 et 20 mg/mmol) possède une excellente valeur prédictive positive pour diagnostiquer une MRC dans 96,80 % des cas. Une évaluation de la relation entre le premier et le deuxième résultat du RAC pour établir une valeur prédictive probable pour une MRC a révélé qu'il était plus probable que la deuxième valeur du RAC soit anormale (≥ 2 mg/mmol) quand le premier résultat était supérieur à 6 mg/mmol, et ce, peu importe qu'il y ait ou non un troisième résultat disponible.
- Il pourrait ne pas être nécessaire de faire plusieurs mesures du RAC pour diagnostiquer une MRC chez un diabétique de type 2 qui présente une microalbuminurie persistante et une MRC. Dans un contexte de soins primaires, le fait de faire plusieurs mesures peut retarder le diagnostic et le dépistage d'une néphropathie diabétique.

Chronic kidney disease (CKD) in diabetes has considerable implications in terms of morbidity and mortality and is associated with both reduced lifespan and lower quality of life.[1,2] There is a higher risk of cardiovascular and all-cause mortality with declining renal function.[3-5] Chronic kidney disease and cardiovascular disease also share common modifiable risk factors including hyperglycemia, hypertension, and hyperlipidemia.[3]

The Diabetes Canada clinical practice guidelines recommend screening for diabetic nephropathy, as early detection and intervention can delay or prevent loss of renal function and progression to end-stage renal disease.[2,6] Diabetic nephropathy is defined as a progressive increase in proteinuria and decline in renal function in patients with diabetes.[2] It is clinically diagnosed as the presence of microalbuminuria or overt nephropathy in patients with diabetes when not explained by other renal diseases.[7]

Microalbuminuria is the earliest clinically detectable stage of diabetic nephropathy defined as urinary albumin of 30 to 300 mg/d or a random urine albumin-to-creatinine ratio (ACR) between 2 and 20 mg/mmol.[8] This level of albumin is below the detection threshold of a urine dipstick.[7,9] Overt nephropathy is defined as a urinary albumin level of greater than 300 mg/d or a random urine ACR of greater than 20 mg/mmol.[7,9]

The Diabetes Canada guidelines recommend screening for CKD with random urine ACR and estimated glomerular filtration rate tests at the time of diagnosis of type 2 diabetes and annually thereafter.[2,6] When the results of the first urine ACR test are between 2 and 20 mg/mmol, 2 out of 3 tests done over a 3-month period showing a persistent elevation in urinary albumin levels are needed to diagnose CKD. Multiple tests to confirm albuminuria are recommended to rule out false-positive results due to alternate causes of transient albuminuria, including considerable exercise, urinary tract infection, fever, congestive heart failure, menstruation, and acute severe elevation in blood glucose or blood pressure.[2,6] Intraindividual day-to-day variability has also been reported.[8] However, the recommendation to repeat an ACR test following abnormal test results between 2 to 20 mg/mmol is largely based on expert opinion, and further research is needed to determine if repeat testing improves diagnostic accuracy.[10]

The RIACE (Renal Insufficiency And Cardiovascular Events) cohort study showed that a single measurement of urinary albumin excretion can accurately predict the nephropathy stage.[11] In the study, a subanalysis was conducted on 4062 of 15 773 patients who had 2 or 3 measures of urinary albumin excretion within a 3- to 6-month period. Among these patients, urinary albumin excretion measurements were obtained from 24-hour urine samples in 833 patients and first-void samples for ACR tests in 3229 patients. The intraindividual coefficient of variation was high at 32.5%. However, the concordance rate between single and the mean of multiple measurements was 94.6% for normoalbuminuria and 90.6% for albuminuria (micro or macro). In another study, a retrospective analysis was done on morning urine samples obtained from 95 patients with type 2 diabetes.[12] In this study 246 triplicate urine ACR test results were analyzed, and the overall concordance rate for albuminuria categorization was 95%. It was determined that repeating a morning urine ACR sample was not necessary in order to categorize patients as having normoalbuminuria, microalbuminuria, or macroalbuminuria. The study did suggest, however, that repeat determinations are necessary for accurate quantification of albuminuria.

These studies suggest that multiple samples might not be necessary at the screening stage for categorizing a patient as having albuminuria or not. However, other studies have shown that multiple samples are still likely necessary to assess changes in urine ACR due to treatment or progression of disease.[13]

Further studies are needed in patients with type 2 diabetes in order to assess if results from the recent studies on reproducibility of a single value of morning urine ACR can be demonstrated with random urine ACR samples. The ability to make a diagnosis using a single sample would avoid the need for a patient to provide time-sensitive or multiple urine samples for screening purposes, and might improve patient compliance for testing and efficiency of implementing interventions in the primary care setting.

Although recent diabetes guidelines recommend initiation of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) therapy independent of the diagnosis of renal disease in patients with diabetes (age ≥ 55 years), the diagnosis remains important, as the presence and progression of renal disease has important implications for pharmacotherapy options and as a cardiovascular risk predictor.[6,14] Accordingly, simplification of the diagnosis of renal disease in the population with type 2 diabetes would have important clinical implications.

With more than 3 million Canadians currently diagnosed with diabetes and with a urine ACR test costing about $11, there could be an economic advantage from a health care utilization perspective of a simpler diagnostic model for CKD in diabetes.[6,15]

Our research objective was to calculate the positive predictive value (PPV) of a single random abnormal urine ACR compared with repeat test results in patients with type 2 diabetes to diagnose CKD. We also explored the relationship between the first and second urine ACR values (between 2 and 20 mg/mmol) when performed within 120 days.

Methods

The study was conducted using secondary data from Calgary Laboratory Services, which is the only

laboratory services provider in Calgary, and therefore these data capture all tests ordered within the region. De-identified data from the laboratory information system were extracted by Alberta Health Services employees and reported to the research team.

The data from January 2008 to December 2015 were assessed to identify patients aged 21 and older with hemoglobin A_{1c} levels of 6.5% or higher or with 2 or more test results revealing fasting plasma glucose levels of 7 mmol/L or higher. To increase the probability of including patients with new-onset type 2 diabetes in the data set, patients were only included if they had a newly recorded hemoglobin A_{1c} (≥6.5%) level or had 2 new recordings of abnormal fasting plasma glucose levels and no abnormal results for these tests recorded in the previous 3 years. To exclude those with gestational diabetes, patients with a previous elevated plasma glucose level when screened with a 50-g glucose tolerance test were not included. The inclusion group was further assessed for a first random abnormal urine ACR result (≥2 mg/mmol) followed by at least 1 other random urine ACR test over a 120-day period. These tests were done as part of routine care. Each patient was included in the data set only the first time he or she met the criteria.

Further analysis was done excluding results when ACEI or ARB therapy was started or adjusted within 3 months before or 4 months after the first urine ACR test to focus our results on screening and not treatment response. This step was completed by linking Calgary Laboratory Services data to Pharmaceutical Information Network data. Pharmaceutical Information Network data contain dispensing data from community and outpatient pharmacies and capture most prescriptions dispensed by Alberta pharmacies.

This project received ethics approval from the Conjoint Health Research Ethics Board at the University of Calgary.

Measures of interest

Logistic regression was used to assess the relationship between the first and second random urine ACR values in order to derive a predictive probability plot. A logistic regression model makes predictions on a log-odds scale, which can be converted to a probability scale. This enabled us to construct a predictive probability plot that showed the probability of the second urine ACR result being positive for a range of ACR values of the first urine ACR (predictor variable).

The PPV of the first urine ACR test result to diagnose CKD was also calculated. The first abnormal urine ACR (≥2 mg/mmol) was considered a true positive if a subsequent positive urine ACR result was obtained within 120 days and a false positive if 2 subsequent negative test results were identified within that time period. Correlation of true positives and false positives with age was assessed using a 2-sample *t* test and with sex using the Pearson χ^2 test.

This analysis was repeated after excluding patients who had ACEI or ARB therapy started or adjusted around the time of the first ACR test.

Statistical analyses were done using R statistical software. A *P* value of less than .05 was considered statistically significant.

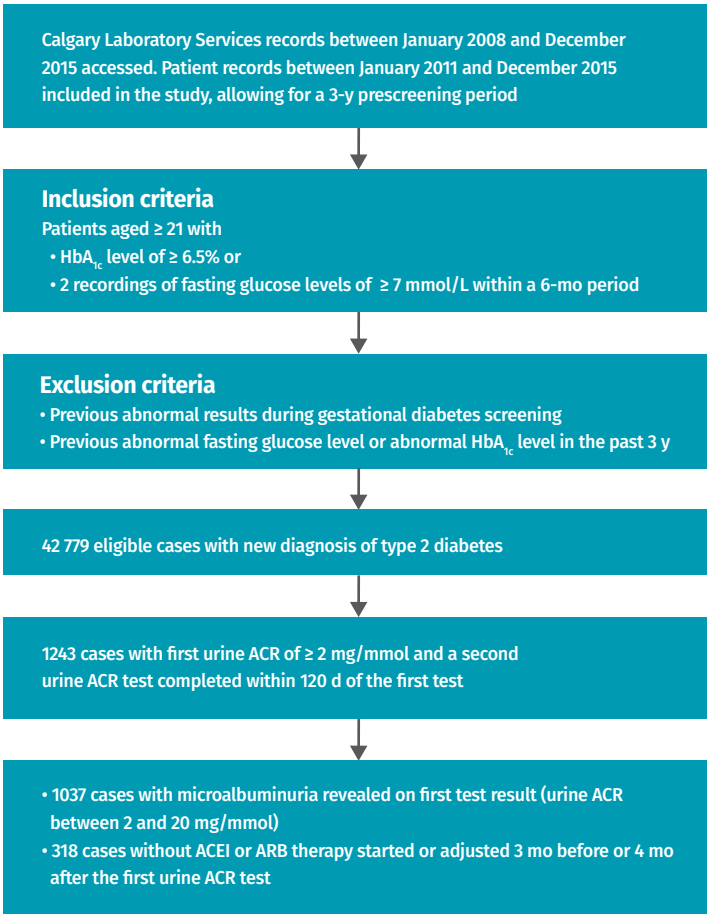
Results

A total of 1243 cases were identified with the inclusion criteria (**Figure 1**); 206 cases in which urine ACR test results revealed values greater than 20 mg/mmol were excluded, as results that reveal macroalbuminuria do not need to be repeated as per Diabetes Canada guidelines.[6] **Table 1** presents the characteristics of the remaining 1037 patients. Analysis was done including all initial positive test results for microalbuminuria to assess how the first urine ACR (2 to 20 mg/mmol) predicts the results of the second urine ACR test. A predictive probability plot was derived from results of logistic regression. **Figure 2** shows the predictive probability plot, which is a graphical representation of the predictive probability of the second urine ACR test being positive for a range of the first urine ACR values. There is increased probability of the second urine ACR being abnormal at higher values of the first urine ACR (2 to 20 mg/mmol), as illustrated in **Figure 2**. The probability of having positive results on the second ACR test is about 0.4 when the first urine ACR is between 2 and 4 mg/mmol and about 0.8 when the first urine ACR is between 6 and 8 mg/mmol.

The PPV of the first urine ACR is calculated based on the Diabetes Canada recommendations that 2 out of 3 positive urine ACR test results in a 3-month period are required to confirm persistent microalbuminuria and diagnose CKD.[6] To calculate the PPV of the first positive urine ACR result to diagnose CKD, it was considered a true positive if another positive test result was identified in the study time frame of 120 days and a false positive if 2 subsequent negative test results were identified in the same time frame. A total of 445 cases that had inadequate follow-up of the first abnormal test result to confirm or refute microalbuminuria were excluded. In the excluded cases, a third urine ACR value was not available when the first urine ACR result was positive but the second urine ACR result was negative.

From 592 remaining cases, 19 were identified as false positive and 573 were identified as true positive, resulting in a PPV of the first abnormal urine ACR (2 to 20 mg/mmol) to diagnose CKD calculated at 96.80% (95% CI 95.37% to 98.21%). There was no statistically significant association with sex ($P=.58$) and no difference in mean age ($P=.51$) between the false-positive and

Figure 1. Flowchart of study sample selection listing inclusion and exclusion criteria



ACEI—angiotensin-converting enzyme inhibitor, ACR—albumin-to-creatinine ratio, ARB—angiotensin II receptor blocker, HbA_{1c}—hemoglobin A_{1c}.

Table 1. Patient characteristics

PATIENTS	N (%)	MEAN (SD) AGE
Male patients	580 (55.9)	55.4 (13.0)
Female patients	457 (44.1)	57.7 (13.8)

true-positive groups. The PPVs for discrete categories of the first urine ACR are presented in **Table 2**.

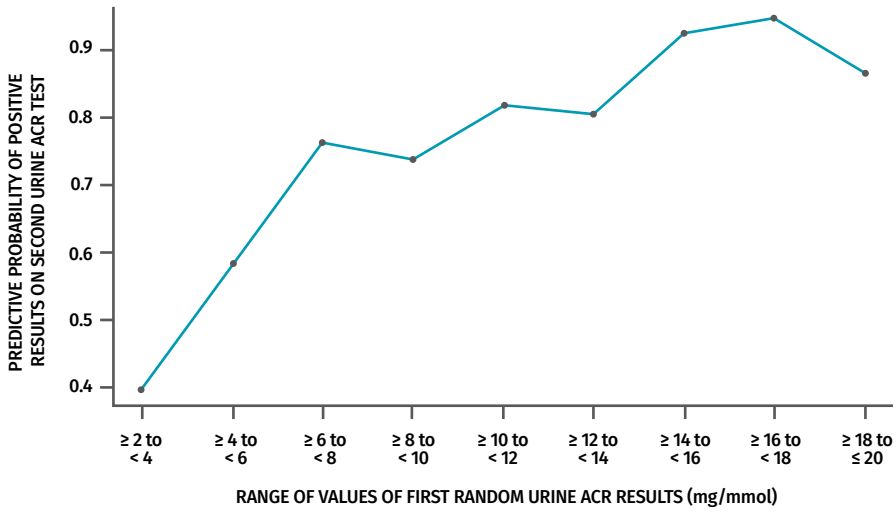
Additional analysis was done after excluding cases in which ACEI or ARB therapy was started or adjusted within 3 months before or 4 months after the first urine ACR test. With these exclusions 318 cases were identified, of which 12 were false positive, resulting in a PPV of first abnormal urine ACR (2 to 20 mg/mmol) of 96.23% (95% CI 94.13% to 98.32%). There was no statistically significant association with sex (P=.84) or difference in mean age (P=.37) between the false-positive and the true-positive groups.

Discussion

Some Canadian studies have previously reported the rate of screening for microalbuminuria in patients with type 2 diabetes in primary care to be below 30%.[16,17] Our study indicates that there is a gap between recommended practice guidelines and clinical practice in follow-up of abnormal urine ACR to screen for CKD in diabetes.

Diabetes Canada recommends that 2 out of 3 abnormal urine ACR results over a 3-month period are required to diagnose CKD.[6] In our analysis, there is a strong PPV for the first abnormal urine ACR (between 2 and 20 mg/mmol) to diagnose CKD at 96.80%. The PPV with exclusion of cases with ACEI or ARB therapy started or adjusted around the first ACR test is similar at 96.23%. We also excluded 445 results in which there were insufficient follow-up data to make a determination if the first abnormal urine ACR was a true positive or a false positive. The number of results with inadequate follow-up indicates a

Figure 2. The predictive probability of the second urine ACR result being positive for albuminuria (≥ 2 mg/mmol) based on a range of values of the first urine ACR result (2-20 mg/mmol) in patients with type 2 diabetes: *The second urine ACR test was done within 120 days of the first urine ACR test.*



ACR—albumin-to-creatinine ratio.

Table 2. The PPV of the first urine ACR to diagnose microalbuminuria, based on urine ACR range

FIRST URINE ACR RANGE, mg/mmol	TRUE POSITIVE,* N	FALSE POSITIVE,† N	PPV (95% CI), %	EXCLUSIONS,‡ N
≥2 to <4	223	11	95.3 (92.6-98.0)	314
≥4 to <6	114	3	97.4 (94.6-100.3)	78
≥6 to <8	73	1	98.6 (96.0-101.3)	22
≥8 to <10	42	2	95.5 (89.3-101.6)	13
≥10 to <12	36	1	97.3 (92.1-102.5)	7
≥12 to <14	29	1	96.7 (90.2-103.1)	6
≥14 to <16	25	0	100.0 (100.0-100.0)	2
≥16 to <18	18	0	100.0 (100.0-100.0)	1
≥18 to ≤20	13	0	100.0 (100.0-100.0)	2
≥2 to ≤20	573	19	96.80 (95.37-98.21)	445

ACR—albumin-to-creatinine ratio, PPV—positive predictive value.
*True positive: a positive urine ACR result was followed by another positive urine ACR result or by 1 negative and 1 positive urine ACR result in 120 days.
†False positive: a positive urine ACR result was followed by 2 negative urine ACR results in 120 days.
‡Exclusions: a positive urine ACR result was followed by a negative urine ACR result but a third value was not available.

gap between guidelines and actual practice. In **Table 2**, it is noteworthy that most of the excluded results occur in the urine ACR range of 2 to 6 mg/mmol and that there is a reduced proportion of excluded results for urine ACR values of 6 to 20 mg/mmol.

We performed an additional analysis looking strictly at the relationship between the first and second urine ACR (irrespective of whether a third value was available) to derive a predictive probability plot. From this analysis, there is greater probability of the second urine ACR result being positive (≥2 mg/mmol) when the first urine ACR is greater than 6 mg/mmol.

Our results suggest that a single random urine ACR might be used to diagnose microalbuminuria or CKD in a patient with type 2 diabetes. Having multiple steps in the diagnostic pathway can negatively affect early detection and screening of diabetic nephropathy in primary care. Reduced steps in screening imply fewer patient visits to the laboratory or to health care providers, which might improve patient compliance and decrease health care expenditure.

Limitations

As previously stated, inadequate follow-up of abnormal urine ACR results, as per guideline recommendations, limited the number of results available to calculate the PPV of the first urine ACR. We also did not assess the relationship between true-positive and false-positive results of first urine ACR and renal function or glycemic control. Our data are limited as this is a retrospective analysis with selection criteria designed to increase the probability of including cases with a new diagnosis of diabetes and a subsequent incident case of abnormal urine ACR. The smaller number of cases obtained secondary to these factors could affect how well the data represent the population with type 2 diabetes. Additional limitations include that we only assessed repeating the urine ACR test for screening. As previous studies indicate, repeat tests are still important to assess progression of disease or treatment response. In our study outcomes related to CKD screening in diabetes were also not examined.

Conclusion

Based on our results, multiple random urine ACR tests might not be necessary to diagnose patients with type 2 diabetes as having persistent microalbuminuria and CKD. A simpler diagnostic model for diagnosing renal disease might improve patient compliance, efficiency of testing, and implementation of health interventions. Reduced testing would also be expected to result in reduced cost from a health care expenditure perspective.

Further studies are required with a greater proportion of triplicate tests available when the second urine ACR result is negative to further assess and confirm the PPV of the first positive urine ACR result.

Dr Garg is Clinical Assistant Professor in the Department of Family Medicine, **Dr Naugler** is Professor and Head of the Department of Pathology and Laboratory Medicine and Professor in the Department of Family Medicine, **Dr Bhella** is Clinical Assistant Professor in the Department of Family Medicine, and **Ms Yeasmin** is a doctoral student in the Department of Mathematics and Statistics, all at the University of Calgary in Alberta.

Contributors

Drs Garg, Naugler, and **Bhella** contributed to the concept and design of the study; data gathering, analysis, and interpretation; and preparing the manuscript for submission. **Ms Yeasmin** contributed to statistical analysis and interpretation, as well as preparing the manuscript for submission.

Competing interests

None declared

Correspondence

Dr Divya Garg; e-mail **dgarg@ucalgary.ca**

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