Hypertension-based clinical risk strategies for detecting microalbuminuria in diabetes

V. BASKAR¹, D. KAMALAKANNAN¹, B. KIBERD², M.R. HOLLAND¹ and B.M. SINGH¹

From the ¹Wolverhampton Diabetes Centre, New Cross Hospital, Wolverhampton, UK, and ²Dalhousie University, Nova Scotia, Canada

Received 23 November 2004 and in revised form 17 March 2005

Summary

Background: Microalbuminuria screening to identify patients at risk of diabetic nephropathy is widely accepted.

Aim: To investigate whether blood-pressure-based strategies can identify such patients without the need for microalbuminuria testing.

Methods: Spot urine for albumin/creatinine ratios was performed in all patients over an 18-month period. The performance of four combinations of clinical models, based on existing triggers for anti-hypertensive intervention (prior use and/or existing systolic BP exceeding 140 or 160 mmHg and/or dipstick proteinuria exceeding 1+ or 2+) was evaluated at microalbuminuria thresholds of 3.5 and 10 mg/mmol. The models were ranked 1 to 4, based on their escalating relative strengths in predicting need for intervention.

Results: Of 3748 patients, 1257 (34%) or 739 (20%) exceeded microalbuminuria thresholds of 3.5 or 10 mg/mmol. All four models predicted microalbuminuria risk (areas under ROC curves 0.60–0.77, all \( p < 0.001 \)). The models (1–4) identified 2220, 2465, 2803 or 2937 for intervention, respectively, irrespective of microalbuminuria status, and missed 368, 232, 194 or 126 at 3.5 mg/mmol and 164, 87, 81 or 45 at 10 mg/mmol.

Discussion: Clinical models using routinely measured parameters reduced the target population for microalbuminuria screening by 60–80%, missing 3–10% of patients with albumin/creatinine ratios exceeding 3.5 mg/mmol or 1–4% of those exceeding 10 mg/mmol.

Introduction

Persistent microalbuminuria (MA) is a marker for the presence of diabetic nephropathy, and effective treatment with anti-hypertensive therapy (AHT) using a variety of agents retards its progression.¹–¹⁰ The natural history of MA, however, is still not well understood. Recent evidences casts considerable doubt on the reliability of MA as a predictor of overt nephropathy.⁵–⁸ Nevertheless, MA is accepted as an important screening tool, and a number of recommendations advocate its routine use in patients with diabetes.¹¹–¹³

Testing for MA, though relatively simple and non-invasive, is fraught with a number of practical difficulties and introduces variables that impact on cost-effectiveness.¹⁴ Those studies that have found screening for MA to be cost-saving have either compared MA screening and intervention against no intervention, or against screening for...
Furthermore, most assumed perfect testing characteristics for MA, and did not consider the impact of false positive results.

In this evaluation, we have examined whether other strategies using readily measured clinical measurements, identify patients with diabetes who will benefit from intervention with anti-hypertensive therapy without the need for MA testing. The models are based on pre-existing treatment with AHT and/or the presence of other compelling indications for such treatment. Four different models with escalating strength in predicting need for intervention were developed and evaluated at two different MA thresholds. Receiver Operator Characteristic (ROC) curves, in which the sensitivity is plotted against the corresponding false positive rate, was used to assess the performance of these clinical risk models. The area under the ROC curve measured how well the models predicted the presence of MA.

### Methods

The diabetes population was drawn from the Wolverhampton district diabetes register, which recorded demographic, clinical and biochemical characteristics of patients on every annual review. The cross-sectional evaluation was done in the 4079 patients who attended the centre over the 18-month period between January 2001 (when universal microalbuminuria screening was commenced in our centre) and June 2002. Of the 4079, MA results were unavailable in 331 individuals, who were excluded from further analysis. There were no other exclusions. Results are presented for the 3748 individuals with MA.

Four combinations of clinical risk models were devised, based on AHT status and two differing thresholds for systolic blood pressure (140 and 160 mmHg) and proteinuria (1+ and 2+) as described in Table 1. The inclusion into the model depended on individuals fulfilling one or the other criteria for triggering AHT. The use of differing thresholds was based on their escalating strengths in predicting adverse risk outcomes. Thus, an SBP threshold of 160 mmHg, with its associated higher absolute risk of vascular events, represented a higher risk group compared to that of 140 mmHg. The Hypertension Optimum Treatment (HOT) Study showed the incidence rates of major cardiovascular events to rise from 18 per 1000 person years at an SBP of 120 mmHg to 24 at >140, 33 at >160 and 37 at >170. With regards to dipstick proteinuria threshold, while 2+ has been found to represent diabetic nephropathy reliably, many patients with 1+ proteinuria are found to have even normoalbuminuria on quantitative testing. Overall, the risk models 1 and 4 thus represented a higher or a lower clinical risk strategy.

The models were used to predict the risk of microalbuminuria for each individual, and the predicted risk was used to construct the ROC curves. There is also a question around the best threshold for MA. An ACR threshold of 10 mg/mmol, with its higher predictive power for overt nephropathy, is believed to represent a better cut-off than 3.5 mg/mmol. We have therefore independently assessed the performance of our models at these two different MA thresholds.

Trained health care professionals carried out blood pressure measurements using automated blood pressure monitors (Dinamap XL, Johnson & Johnson). Urine dipstick for protein was done (Combur5 Test D strips, Roche Diagnostics) and the results read visually as negative or positive at 1+, 2+ or greater, representing protein concentrations of <30, >30, 100 and 500 mg/dl, respectively. Microalbuminuria screening was done using spot morning urine for albumin/creatinine ratio (ACR), in accordance with the recommendations of the American Diabetes Association. Urine creatinine (mmol/l) was quantitated by the Jaffe method (Roche Modular System) and urine microalbumin (mg/l) by immunoassay (Microalbumin Immulite, DPC).

Statistical analyses were performed using version 10 of the Statistical Package for Social Sciences (SPSS) and were considered significant at the 5% level. Approval from the Local Research and Ethics committee was obtained for this evaluation.

### Table 1 Definitions of clinical risk models based on prior use of anti-hypertensive therapy and/or presence of untreated hypertension and/or overt proteinuria as defined below

<table>
<thead>
<tr>
<th>Model</th>
<th>Systolic BP threshold</th>
<th>Dipstick proteinuria threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>160</td>
<td>2+</td>
</tr>
<tr>
<td>2</td>
<td>160</td>
<td>1+</td>
</tr>
<tr>
<td>3</td>
<td>140</td>
<td>2+</td>
</tr>
<tr>
<td>4</td>
<td>140</td>
<td>1+</td>
</tr>
</tbody>
</table>
Results

The mean age of the cohort was 59 years; 57% were males. The majority (76%) had type 2 diabetes, and the ethnic breakdown was 67% Caucasian, 24% Indo-Asian and 9% Afro-Caribbean. Prior use of anti-hypertensive therapy was seen in 1872/3748 (50%). A further 902 (24%) or 294 (8%) had existing SBP exceeding thresholds of 140 or 160 mmHg, respectively, that was currently untreated. Overall, 932/3748 (25%) or 247 (7%) had overt nephropathy at dipstick thresholds of 1+ or 2+, respectively.

Regarding MA results, 2491/3748 (66%) had normoalbuminuria (ACR < 3.5 mg/mmol), 513 (14%) had lower risk MA (ACR 3.5–10 mg/mmol), 345 (9%) had higher risk MA (ACR 10–30 mg/mmol) and the remaining 399 (11%) had overt nephropathy (ACR > 30 mg/mmol). Thus 1257 (34%) or 744 (20%) had abnormal albuminuria at ACR thresholds of 3.5 and 10 mg/mmol, respectively.

The ROC curves displaying the performance of the above-described clinical models at ACR thresholds of 3.5 and 10 mg/mmol, and the corresponding areas under the curves (AUC), are shown in Figures 1 and 2 respectively. The unselected residual population, sensitivity, specificity, positive and negative predictive values, and the numbers with MA missed after the application of these models are shown in Table 2 (ACR threshold 3.5 mg/mmol) and Table 3 (ACR threshold 10 mg/mmol).

At both the ACR thresholds, all four models appeared to significantly predict the risk of MA (all \( p < 0.001 \)), the performance being relatively better at a threshold of 10 mg/mmol. With respect to AUC, the models that incorporated dipstick threshold of 1+ performed better than the other models.

After the application of these clinical models, the residual unselected populations were 1528/3748 (41%) using model 1, 1283 (34%) using model 2, 945 (25%) using model 3 and 811 (22%) using model 4. Thus the use of MA screening would not have triggered intervention over and above the clinical strategy in 60–80% of the population.

At an ACR threshold of 3.5 mg/mmol, the numbers of patients with MA that these models (1 to 4) missed were 368, 232, 194 and 126, representing 10%, 6%, 5% and 3% of the whole study population, respectively (false negative rates). The equivalent values at ACR threshold of 10 mg/mmol were 164, 87, 81 and 45, representing 4%, 2%, 2% and 1%, respectively, of the study population. The lower false negative rates reflected on their relatively good sensitivity and negative predictive value rates. Although the models’ high false positive rates impacted on their poor specificity and positive predictive value rates, since the inclusion into the model was based on the presence of valid triggers for AHT, the false positives would only be for nephropathy and not for intervention.

Thus, even without MA testing, the highest (model 1) and lowest (model 4) clinical risk

![Figure 1](https://academic.oup.com/qjmed/article-abstract/98/6/427/1548132/1.56812)
models missed only 10% and 3% of patients with ACR exceeding 3.5 mg/mmol and 4% and 1% of those with ACR exceeding 10 mg/mmol, respectively.

Discussion

Microalbuminuria is now accepted as a useful screening tool to identify patients at risk of diabetic nephropathy, who may therefore benefit from effective intervention with anti-hypertensive drugs. The natural history of microalbuminuria, however, is poorly understood. While earlier evidence showed it to have high predictive values for overt nephropathy, more recent trials seriously question this. Testing for MA is also fraught with some practical difficulties, and strategies to overcome them impose a significant burden on patient management and cost-effectiveness, without necessarily improving diagnostic certainty. Furthermore, in the absence of evidence on the usefulness of MA testing in patients already established on AHT, the value of annual re-screening is also questioned. The proportion of patients likely to benefit from such testing in the subsequent years of screening will be smaller, approaching the annual incidence rate of MA (1–4%).

The need for optimal blood pressure control and attention to vascular risk factors in patients with diabetes is now well understood. There are readily available clinical parameters that identify at risk patients for intervention with AHT and taking these into account, the additional impact that the detection of MA will have, is not known. The thresholds of these parameters (hypertension or overt nephropathy) when intervention is indicated can vary depending on their relative ability in predicting adverse events. Thus a SBP threshold of 160 mmHg identifies a group at a higher risk for adverse events, compared to a threshold of 140 mmHg, and the same argument can be applied to the choice of dipstick proteinuria thresholds (2+ versus 1+). On the question of the appropriate threshold to define significant MA, it can still be argued, as it has been by others, that an ACR of 10 mg/mmol, with its higher predictive power for overt nephropathy, is a better cut-off than 3.5 mg/mmol.

We have addressed these issues by using four different clinical approaches at two different ACR thresholds. Our results show that the use of readily available clinical parameters to trigger AHT can reduce the target population likely to benefit from MA screening by 60–80%. In the first year of screening, even without MA testing, we would have missed only 3–10% and 1–4% of the population with ACR >3.5 and >10 mg/mmol, respectively, depending on the model chosen. Significant proportions of these are likely to fulfil our clinical criteria for intervention in the subsequent years.

While many cost-benefit analyses concluded MA screening in diabetes to be cost-saving, they either compared MA screening and intervention...
against no intervention or against screening for macroalbuminuria only.\textsuperscript{15–18} Furthermore, most studies assumed perfect testing characteristics for MA and did not consider the impact of false positive results. However, one study has considered false positives as well as comparing MA screening strategy to a hypertension and/or macroalbuminuria strategy.\textsuperscript{15} It concluded that for MA screening to be cost-effective, the proportion of those with concomitant hypertension ought to be $<$64%, and the positive predictive value of MA test had to be at least 0.8. Formal cost-benefit analyses will be needed to answer the question as to which of our models is the most cost-effective. However, with a significant proportion of our population (74% or 58%, using SBP thresholds of 140 or 160 mmHg, respectively) already noted to have hypertension that would benefit from intervention irrespective of the albuminuria status, the additional value of MA screening is already strongly questioned.

The value of routine screening for dipstick proteinuria can also be similarly argued. However, dipstick screening is already part of routine care

Table 2 Performance of clinical models 1–4 in predicting need for microalbuminuria intervention at albumin/creatinine ratio (ACR) threshold of 3.5 mg/mmol in a clinic population with diabetes universally screened for microalbuminuria (MA) ($n=3748$)

<table>
<thead>
<tr>
<th>Model...</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number with MA</td>
<td>1257</td>
<td>1528</td>
<td>368</td>
<td>164</td>
</tr>
<tr>
<td>Number identified for anti-hypertensive intervention (% of base population)</td>
<td>(59%)</td>
<td>(66%)</td>
<td>(75%)</td>
<td>(78%)</td>
</tr>
<tr>
<td>Number excluded by model as not requiring intervention (% of base population)</td>
<td>(41%)</td>
<td>(34%)</td>
<td>(25%)</td>
<td>(22%)</td>
</tr>
<tr>
<td>Number with MA missed after application of model (% of base population)</td>
<td>(10%)</td>
<td>(6%)</td>
<td>(5%)</td>
<td>(3%)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>71%</td>
<td>82%</td>
<td>85%</td>
<td>90%</td>
</tr>
<tr>
<td>Specificity</td>
<td>47%</td>
<td>42%</td>
<td>30%</td>
<td>27%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>40%</td>
<td>42%</td>
<td>38%</td>
<td>39%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>76%</td>
<td>82%</td>
<td>79%</td>
<td>84%</td>
</tr>
</tbody>
</table>

Table 3 Performance of clinical models 1–4 in predicting need for microalbuminuria intervention at albumin/creatinine ratio (ACR) threshold of 10 mg/mmol in a clinic population with diabetes universally screened for microalbuminuria (MA) ($n=3748$)

<table>
<thead>
<tr>
<th>Model...</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number with MA</td>
<td>744</td>
<td>1528</td>
<td>164</td>
<td>164</td>
</tr>
<tr>
<td>Number identified for anti-hypertensive intervention (% of base population)</td>
<td>(59%)</td>
<td>(66%)</td>
<td>(75%)</td>
<td>(78%)</td>
</tr>
<tr>
<td>Number excluded by model as not requiring intervention (% of base population)</td>
<td>(41%)</td>
<td>(34%)</td>
<td>(25%)</td>
<td>(22%)</td>
</tr>
<tr>
<td>Number with MA missed after application of model (% of base population)</td>
<td>(4%)</td>
<td>(2%)</td>
<td>(2%)</td>
<td>(1%)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>78%</td>
<td>88%</td>
<td>89%</td>
<td>94%</td>
</tr>
<tr>
<td>Specificity</td>
<td>45%</td>
<td>40%</td>
<td>29%</td>
<td>25%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>26%</td>
<td>27%</td>
<td>24%</td>
<td>24%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>89%</td>
<td>93%</td>
<td>91%</td>
<td>94%</td>
</tr>
</tbody>
</table>
provided to diabetic patients, and apart from being easy to use, they are also considerably cheaper than MA. Furthermore, dipstick proteinuria hierarchically represents a later stage of nephropathy with an increased likelihood of inevitable progression to end stage renal disease and although the reliability of dipsticks at 1+ threshold has been questioned, there is no problem with false negativity or positivity at thresholds of 2+ or more.

The observed excess cardiovascular risk in individuals with albuminuria (especially with type 2 diabetes) is quoted as another reason to justify microalbuminuria screening. The relationship between microalbuminuria and cardiovascular risk is complex, and there is little evidence that the link is causal. Rather, it is thought that MA and cardiovascular risk are likely to be downstream expression of common aetiological factors. There are well-validated risk engines to calculate cardiovascular risk, and none of these include MA in their calculations, so microalbuminuria cannot be logically used to predict cardiovascular risk.

As to which of our clinical strategies one follows, this is up to the service providers after fully understanding risk evaluation. Whichever model one pursues, we have shown the detection of MA to have little or no additional impact in 60–80% of the population. The fact that, even without MA testing, our best-performing clinical model would have missed only 1–3% of the study population with significant MA, strongly questions the value of MA screening. Formal cost-benefit analysis will be required to answer this question fully. Our study hopefully stimulates the need for continuing debate on how best to use MA testing.

Acknowledgements

This study was supported by a grant from the South Staffordshire Medical Foundation, UK.

References


