ORIGINAL ARTICLE

Microalbuminuria screening for patients having type 2 diabetes mellitus: Who wants to participate?

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Medical subject headings: albuminuria; diabetes mellitus, non-insulin-dependent; diabetic nephropathies; patient selection

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Abstract

Background and objectives: “Difficult-to-recruit” patients are sometimes less compliant with their care, are more reluctant to seek medical attention and less likely to survive than their “easy-to-recruit” counterparts. They also tend to be excluded from clinical trials. The aim of this paper was to evaluate whether such differences extend to patients’ willingness to be screened for diabetic nephropathy in a family practice setting.

Design: A cross-sectional study.

Setting: A Canadian university family practice unit.

Patients: Two hundred and forty-seven patients with type 2 (adult-onset) diabetes mellitus as identified by computer searches of patient records of approximately 12 000 patients in the family practice unit.

Intervention: A cross-sectional secondary preventive screening program obtained urine samples from all patients with type 2 diabetes mellitus, regardless of patients’ willingness to participate.

Main outcome measure: The prevalence of micro- and macroalbuminuria.

Results: Of the 247 patients identified, 186 (75%) easy-to-recruit enrollees agreed to participate in screening and 61 (25%) difficult-to-recruit non-enrollees initially declined to be screened. The non-enrollees were subsequently evaluated by their own family physicians as part of routine clinical care and the results were captured for analysis. Overall rates of albuminuria were similar in the easy- and difficult-to-recruit groups (31% versus 38%, p = 0.151). The main predictors of albuminuria were female sex (odds ratio [OR] = 2.1, p = 0.021), duration of diabetes in years (OR = 1.05, p = 0.023), current use of angiotensin-converting enzyme inhibitor (OR = 2.26, p = 0.008) and number of diabetic complications (OR = 1.45, p = 0.028).

Conclusions: There is little difference in the prevalence of albuminuria related to patients’ willingness to participate in a screening program. Therefore, there are no disproportionate gains for family practice researchers who aggressively seek difficult-to-recruit patients in this set-
Principale mesure de résultats : La prévalence de la micro-albuminurie et de la macro-albuminurie.

Résultats : Sur les 247 patients identifiés, 186 (75 %) inscrits faciles à recruter ont consenti à se soumettre au dépistage et 61 (25 %) non inscrits difficiles à recruter ont refusé au début de le faire. Les non-inscrits ont été évalués par la suite par leur propre médecin de famille dans le cadre de soins cliniques de routine et l’on a saisi les résultats de l’évaluation pour analyser. Les taux globaux d’albuminurie étaient semblables chez les sujets faciles à recruter et chez les difficiles à recruter (31 % contre 38 %, p = 0,151). Les principaux prédicteurs de l’albuminurie étaient le sexe féminin (coefficient de probabilité [CP] = 2,1, p = 0,021), la durée du diabète en années (CP = 1,05, p = 0,023), l’utilisation courante de l’inhibiteur de l’enzyme de conversion de l’angiotensine (CP = 2,26, p = 0,008) et le nombre de complications attribuables au diabète (CP = 1,45, p = 0,028).

Conclusions : Il y a peu de différence dans la prévalence de l’albuminurie liée à la participation des patients à un programme de dépistage. Il n’y a donc pas de gains disproportionnés pour les chercheurs en médecine familiale qui cherchent sciemment des patients difficiles à recruter dans ce contexte. Par ailleurs, les médecins de premier recours devraient faire tous les efforts possibles pour assurer un soin optimal aux patients diabétiques, sans égard à l’hésitation initiale du patient.

Table 1: Recruitment in several clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients screened</th>
<th>No. (and %) of patients randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDFP Cooperative Group</td>
<td>178 009</td>
<td>10 940 (6)</td>
</tr>
<tr>
<td>Hass et al, 1989§</td>
<td>8 814</td>
<td>3 069 (35)</td>
</tr>
<tr>
<td>Shepherd et al, 1995§</td>
<td>81 161</td>
<td>6 595 (8)</td>
</tr>
<tr>
<td>Redelmeier et al, 1995</td>
<td>283</td>
<td>133 (47)</td>
</tr>
</tbody>
</table>

HDFP = Hypertension Detection and Follow-up Program.
quires strict control, ongoing surveillance and a high degree of patient compliance. One diabetic complication, nephropathy, is becoming the leading cause of end-stage renal disease in the developed world. Microalbuminuria is a sensitive marker for early nephropathy and a strong predictor of long-term mortality. Moreover, interventions such as angiotensin-converting enzyme (ACE) inhibition, directed at microalbuminuria may delay the progression to renal failure. Therefore, microalbuminuria screening by family doctors is important in diabetic patients. The degree of non-compliance in clinical practice is relatively unknown. The present study aims to evaluate whether there is a differential prevalence of diabetic albuminuria based on the patients’ willingness to participate in a preventive screening program.

Methods

Study patients were drawn from the Family Practice Unit of Sunnybrook and Women’s College Health Science Centre, a teaching health-services organization of the University of Toronto with approximately 12,000 patients. Subjects were identified by computer searches of all clinic visits between Jan. 1, 1994, and June 30, 1996, that were classified with the Ontario Health Insurance Plan diagnostic code for “diabetes” (no. 250). A chart review of those patients identified was conducted to verify eligibility and to record relevant clinical information (demographic characteristics, duration of diabetes, current treatment regimens, medications and relevant laboratory results).

Letters of introduction were sent to all eligible patients who were aged 18 years or older and had type 2 (adult-onset) diabetes mellitus. The main intent of the letter was to introduce the study and emphasize its importance and the role for participants. The letters were followed by telephone calls to arrange for an interview. Those who declined to be screened or did not respond to a maximum of 5 rounds of letters and follow-up telephone calls within 6 months were grouped into the DTR category. Patients who were willing to be screened were grouped in the ETR category, regardless of when they agreed.

Enrollees (ETR group) were scheduled for an interview at which a research assistant recorded demographic details, weight, blood pressure and clinical information relating to the patient’s diabetic condition and associated complications. Mean blood pressure readings used in the analysis were calculated from 3 consecutive measurements over 15 minutes documented at the time of the interview. Patients were also asked to bring in a first morning urine sample for microalbumin screening. Subjects who tested negative were asked to return for annual re-screening. Subjects who tested positive were asked to provide timed overnight urine samples on 2 further separate occasions for confirmation.

Urine samples were tested for albumin by nephelometry and for creatinine by the Jaffé reaction. Patients were classified into 3 categories: normal (urinary albumin:creatinine ratio <2.5 mg/mmol for men, <3.5 mg/mmol for women), microalbuminuric (urinary albumin:creatinine ratio 2.5 to 24 mg/mmol for men, 3.5 to 34 mg/mmol for women and macroalbuminuric (urinary albumin:creatinine ratio ≥25 mg/mmol for men, ≥35 mg/mmol for women). True micro- or macroalbuminuria was defined as at least 2 positive tests out of 3 samples over a period of less than 3 months. Non-enrollees (DTR group) were evaluated by their own family physicians who were asked to perform urine screening and blood pressure measurements according to the same criteria.

The main outcome measure was the prevalence of diabetic albuminuria in DTR non-enrollees compared with ETR enrollees. We performed a backwards, stepwise logistic regression analysis to determine additional independent predictors of albuminuria. Independent predictors considered included age, sex, race, smoking, duration of diabetes, poorly-controlled blood pressure, current treatment with ACE inhibitors, glycosylated hemoglobin (Hb A1c) level, number of diabetic complications and a dichotomous dummy variable for ease of recruitment. These variables have been shown to be epidemiologically and biologically linked to albuminuria and nephropathy in previous studies. The probability value to eliminate a predictor from the final model was set at 0.05. All p values were 2-tailed and not adjusted for multiple comparisons. We also performed a similar multivariate regression analysis to examine the independent predictors of recruitment. Predictors considered in this analysis were the same as in the previous model.
This research was approved by the hospital ethics committee, including capture of the results from clinical records to incorporate into the present report.

**Results**

Of the approximately 12,000 patients enrolled in the family practice unit, 247 patients with type 2 diabetes mellitus were identified by computer searches of patient records. Of these, 186 (75%) ETR enrollees agreed to participate in screening and 61 (25%) DTR non-enrollees declined to be screened. Three (5%) of the 61 patients in the DTR group were lost to follow-up due to serious psychiatric illness and were excluded from the analysis; the remaining 58 were screened by their family doctors and included in the analysis (Table 253,36).

A total of 79 patients had albuminuria. The rate of albuminuria was similar in the ETR and DTR groups (31% versus 38%, \( p = 0.151 \)). Using a 2-tailed alpha level of 0.05 and sample sizes of 58 and 186 for the DTR and ETR groups respectively, calculations suggest that we had 95% power to detect statistically significant differences if the rates were around 70% and 43%.37 However, authorities suggest that the confidence interval method is more appropriate for similarity than post-hoc calculations.38 We calculated the 95% confidence interval (CI) around the observed difference of 7.2%, yielding −7% to 21%. Thus, a large difference in rates of albuminuria between the 2 groups is unlikely.

In the multivariate logistic regression model, the independent predictors of albuminuria were female sex, duration of diabetes, number of diabetic complications and current use of ACE inhibitors (Table 3). As in the bivariate analysis, the ease of recruitment (DTR versus ETR) did not influence the outcome of albuminuria status in our model \( (p = 0.45) \). Age and race were not retained in the final model, nor were the presence of hypertension, Hb A1c level and smoking. In an additional regression analysis, where recruitment was the outcome variable, only the Hb A1c level was found to be positively associated with difficult recruitment. Each 0.01 unit increase in Hb A1c was associated with an odds ratio of 0.85 \( [0.73 \text{ to } 0.98, \ p = 0.022] \).

No single characteristic, or combination of characteristics, reliably identified patients who would be

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**Table 2: Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Easy to recruit ((n = 186))</th>
<th>Difficult to recruit ((n = 58))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (and SD) age, yr</td>
<td>69 (11)</td>
<td>69 (13)</td>
</tr>
<tr>
<td>Female sex</td>
<td>111 (60)</td>
<td>30 (52)</td>
</tr>
<tr>
<td>White race</td>
<td>164 (88)</td>
<td>49 (84)</td>
</tr>
<tr>
<td>Smoking status†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>23 (12)</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>71 (38)</td>
<td>28 (48)</td>
</tr>
<tr>
<td>Never a smoker</td>
<td>92 (49)</td>
<td>22 (38)</td>
</tr>
<tr>
<td>Mean (and SD) duration of NIDDM since diagnosis, yr</td>
<td>8 (7)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Mean (and SD) blood pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>141 (17)</td>
<td>145 (20)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>78 (9)</td>
<td>79 (9)</td>
</tr>
<tr>
<td>Poorly-controlled blood pressure‡</td>
<td>96 (52)</td>
<td>37 (64)</td>
</tr>
<tr>
<td>Mean (and SD) Hb A1c level</td>
<td>0.078 (0.020)</td>
<td>0.085 (0.020)</td>
</tr>
<tr>
<td>Current medications§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>62 (33)</td>
<td>29 (50)</td>
</tr>
<tr>
<td>Other antihypertensive agents</td>
<td>74 (40)</td>
<td>36 (62)</td>
</tr>
<tr>
<td>Diabetic complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinopathy</td>
<td>21 (11)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>23 (12)</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>63 (34)</td>
<td>24 (41)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>88 (47)</td>
<td>36 (62)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>25 (13)</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Foot ulcers</td>
<td>18 (10)</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Mean (and SD) diabetic complication count**</td>
<td>0.8 (0.9)</td>
<td>1.0 (1.0)</td>
</tr>
<tr>
<td>Degree of albuminuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein negative</td>
<td>129 (69)</td>
<td>36 (62)</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>44 (24)</td>
<td>12 (21)</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>13 (7)</td>
<td>10 (17)</td>
</tr>
</tbody>
</table>

*Figures are no. (and %) except where indicated.
†Percentages may not total 100 because of rounding.
‡Defined as mean systolic \( \geq 140 \) mm Hg or mean diastolic \( \geq 90 \) mm Hg.35,36
§Percentages may not total 100 because of concurrent medications.
**Total number of individual complications in each patient.
NIDDM = noninsulin-dependent diabetes mellitus, ACE = angiotensin-converting enzyme.

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**Table 3: Main predictors of albuminuria**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds ratio (95% CI)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>2.06 (1.13–3.85)</td>
<td>0.021</td>
</tr>
<tr>
<td>Duration of diabetes, yr</td>
<td>1.05 (1.01–1.10)</td>
<td>0.023</td>
</tr>
<tr>
<td>Current use of ACE inhibitors</td>
<td>2.26 (1.24–4.15)</td>
<td>0.008</td>
</tr>
<tr>
<td>Diabetic complication count*</td>
<td>1.45 (1.05–2.04)</td>
<td>0.028</td>
</tr>
<tr>
<td>Recruitment (DTR v. ETR)†</td>
<td>0.77 (0.39–1.54)</td>
<td>&gt;0.20</td>
</tr>
</tbody>
</table>

*Obtained by summing the number of individual complications in each patient.
†Recruitment forced into logistic regression model.
ACE = angiotensin-converting enzyme, DTR = difficult to recruit, ETR = easy to recruit.
free of albuminuria. For example, of the 165 patients without albuminuria 53\% were hypertensive, whereas 61\% of those with albuminuria had hypertension \((p = 0.30)\). There was no significant difference in the rates of hypertension between the ETR and DTR groups (rate difference, 11\%; 95\% CI, 4\% to 26\%). Furthermore, 94\% of hypertensive patients with albuminuria were on antihypertensive medications (diuretics, β-blocking agents, ACE inhibitors or calcium-channel antagonists) compared with 92\% of those without albuminuria \((p = 0.49)\).

Discussion

We found no large difference in the prevalence of albuminuria between the ETR and DTR groups in a large university-affiliated family practice unit. Overall, about one-third of the ETR group was identified as being either micro- or macroalbuminuric, thereby potentially facilitating timely management of the underlying nephropathy, delaying the progression of renal disease and perhaps even avoiding the losses associated with end-stage renal disease.\(^{29}\) As a corollary, however, an equal proportion of DTR patients had some degree of albuminuria that might otherwise not have been identified in the absence of screening. These results underline the importance of universal screening in the diabetic population. The prevalence of micro- and macroalbuminuria in our study is consistent with that reported in other primary care-based as well as population-based studies.\(^{34,39}\)

In both the bivariate and multivariate analyses, we have shown that the present study was adequately powered to rule out any large difference between the ease of recruitment and albuminuria. However, it should be noted that the study may not have had sufficient power to detect potentially small differences between all other possible risk factors and albuminuria, although Table 3 reveals that the regression analysis had identified most other known risk factors for albuminuria.\(^{34}\)

Of note, hypertension did not predict albuminuria in these patients. This suggests that normotensive diabetic patients are just as likely to have albuminuria as their hypertensive counterparts, reaffirming previous calls to screen and treat diabetic normotensive patients as aggressively as diabetic hypertensive patients.\(^{35,36,40–43}\) Moreover, age, race, smoking history and Hb A\(_1c\) levels were not independently predictive of albuminuria, suggesting that clinicians may need to be aware of the possibility of nephropathy in all diabetic patients. These results also point to an interesting interplay between human biology and psychology. Although the psychological mechanisms are obviously dissimilar in DTR and ETR patients, the biologic processes underlying diabetic nephropathy seem to work in the same manner for all patients.

Previous research has identified various factors distinguishing ETR from DTR patients in both research and clinical-practice settings. Advanced age, low socioeconomic level, use of alcohol or tobacco, high subjective and perceived risks of major illness have often been cited as barriers to recruitment.\(^{7,10,16,23,44}\) Specifically for screening interventions, it has been reported that patients who have never been screened for the condition studied, previous low health-services utilization, perceived barriers to access, lack of exposure to health-education interventions and belief in the incurability of the condition are additional predictors for non-attendance at screening.\(^{35–38}\) In the present study, however, an elevated Hb A\(_1c\) level was the only characteristic over-represented in the DTR group. Our failure to identify other associations may reflect a relatively small sample size. Moreover, the study is cross-sectional in nature and thus subject to the usual limitations related to selective sampling, hidden confounders and ambiguous temporality. Finally, Hb A\(_1c\) may itself be a surrogate for low socioeconomic level and other barriers.

Other potential limitations bear mention. We may have missed some diabetic patients despite a rigorous computer search, if family physicians did not label all diabetic patients’ visits with the code for “diabetes.” In addition, our practice setting, although primary care-based, is physically situated within a tertiary care hospital affiliated with a medical school. The characteristics of our patient population as detailed in Table 2 do not appear to be entirely consistent with those of Canadian diabetic patients as revealed by population-based surveys.\(^{51,52}\) Thus, this sample may not necessarily be representative of the Canadian diabetic population at large, and this could affect the generalizability of the results to other settings. Although not immediately applicable to other practice settings, our findings...
suggest the need for further confirmation of these data in other population groups. Lastly, this study did not address the potential predictors of responsiveness to therapy for nephropathy, although other studies have shown that ACE inhibition worked uniformly regardless of patient characteristics and risk factors.40–43 The most compelling question for future research is the responsiveness to treatment in DTR and ETR patients receiving medical therapy.

Clinician-scientists often focus on sample size without paying as much attention to the representativeness of the patients, the recruitment rate, the ease of recruitment and the healthy-volunteer effect. This makes the interpretation of much of the evidence-based literature difficult and casts some doubt on the generalizability to DTR patients. In light of the results from the present study, we conclude that there appears to be little gain for researchers who aggressively seek reluctant patients in a primary care setting. In contrast, clinicians should make every effort to ensure optimal care for patients regardless of their initial hesitancy.

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Competing interests: none stated.

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