BACKGROUND: Microalbuminuria (MA) is recognized as an important risk factor for cardiovascular and renal complications in diabetes. We sought to evaluate how screening for MA is conducted and how urine albumin (UA) results are interpreted in primary care internationally.

METHODS: General practitioners (GPs) received a case history–based questionnaire depicting a male type 2 diabetes patient in whom UA testing had not been performed. Questions were related to type of urine sample used for UA testing, need for a repeat test, whether UA testing was performed in the office laboratory, and what changes in UA results were considered clinically important [critical difference (CD)]. Participants received national benchmarking feedback reports.

RESULTS: We included 2078 GPs from 9 European countries. Spot urine samples were used most commonly for first time office-based testing, whereas timed collections were used to a larger extent for hospital-based repeat tests. Repeat tests were requested by 45%–77% of GPs if the first test was positive. Four different measurement units were used by 70% of participants in estimating clinically important changes in albumin values. Stated CDs varied considerably among GPs, with similar variations in each country. A median CD of 33% was considered clinically important for both improvement and deterioration in MA, corresponding to an achievable analytical imprecision of 14%, when UA is reported as an albumin/creatinine ratio.

CONCLUSIONS: Guidelines on diagnosing MA are followed only partially, and should be made more practicable, addressing issues such as type of samples, measurement units, and repeat tests.

The burden of diabetes is increasing worldwide, especially type 2 diabetes, which is usually treated in a primary health care setting. It is estimated that 180 million people suffer from diabetes, but this number will probably double by 2030 (1, 2). Cardiovascular disease and end-stage renal disease are among the most severe long-term complications of diabetes, and microalbuminuria (MA) (3) is recognized as an important risk factor for the occurrence of both complications (3). Because medical treatment reducing the risk of complications is available, urine albumin (UA) is especially recommended as a screening test for diabetes patients (4–7), although it is increasingly recommended also for the early recognition of renal disease and cardiovascular risk stratification (8, 9).
Several testing methods are used to detect low concentrations of UA. Measurements of albumin excretion in timed collections (overnight or 24-h), albumin morning or random concentration, and as an albumin/creatinine ratio (ACR) (to correct for variation in diuresis) are recommended. Thus, 4 different quantities with 4 corresponding measurement units are used for UA testing (4–7). Further, at least 2 positive results are needed to diagnose MA. The resulting complexity of guidelines may cause difficulties implementing UA testing in everyday practice in primary care, and misinterpretation of results may lead to incorrect treatment of diabetes patients.

At the Norwegian Quality Improvement of Laboratory Services in Primary Care (NOKLUS), a case-history model to study requisition and interpretation of laboratory tests has been developed as a tool for post-analytical external quality assurance. The general practitioner (GP) is asked to evaluate a test in a recognizable clinical situation by responding to a short questionnaire. The model has been applied on several occasions, including an earlier international survey on blood glucose and HbA1c (10). Despite detailed guidelines on how MA screening should be performed (4–7), and many studies evaluating the extent to which testing is done (11–14), little information is available on how GPs actually conduct testing.

The aim of this study was to explore and assess the use and implementation of UA in primary care in different regions, and whether availability of office equipment influenced GPs’ decisions. In addition, we evaluated what changes in UA results GPs considered to be clinically important.

Materials and Methods

In 2006, we mailed a case history–based questionnaire to GPs in 10 European countries and Australia (see Supplemental Fig. 1 in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol54/issue10). The survey was designed and coordinated by NOKLUS and by the IFCC Global Campaign on Diabetes Mellitus.

Based on feasibility, GPs were recruited by national coordinators sending the questionnaire either to GPs in nearby counties or to GPs cooperating with their own or collaborating clinical chemistry laboratories (in Croatia, Denmark, Estonia, France, and the Netherlands). Questionnaires in Hungary were distributed through educational networks; those in Sweden, Norway, Spain, and Austria through participation in External Quality Assessment Schemes; and those in Australia by including the questionnaire in a pathology newsletter. In Sweden, the questionnaire was sent to GP surgeries to be forwarded to individual GPs. Coordinators were asked to recruit between 200 and 600 GPs, whereas in Norway the questionnaire was sent to all GPs. A reminder was distributed in all countries except Australia and Austria.

Because UA examination is probably most well established for diabetes patients, the case history was formulated on the profile of a male type 2 diabetes patient in whom UA testing had not been performed. The profile was based on patient records of a GP with experience in delivery of diabetes care and formulation of such questionnaires, with special emphasis on face validity. Questions were related to methods for measurement of UA, need for a repeat test, and clinically important changes in UA results. Also obtained was information regarding GPs’ age, sex, whether tests for UA were regularly requested, and availability of office-based test methods for UA. The case history and questions posed were peer reviewed twice and commented on by academic staff at the Section for General Practice, Department of Public Health and Primary Health Care, University of Bergen, Norway. The survey questionnaire was successfully pilot-tested among 167 GPs in Norway. Finally, the suitability of the questionnaire for implementation was reviewed by experts in each participating country, a process that resulted in only a few minor changes.

NOKLUS provided all collaborators with the questionnaire and suggestions for a standard covering letter, as well as a reminder notice, in English. Each collaborating unit translated the material to their native language and distributed it with a deadline of 10 days, after which one reminder was sent.

Replies were registered into a custom-designed Web-based application, accessible only using country-specific usernames and passwords. These data were processed by country, and example feedback reports in English were provided by NOKLUS to national study coordinators who reviewed and edited the medical contents and provided translations as needed. Finalized reports were identified with unique ID numbers and made available on the Web application. National study coordinators downloaded, printed, and returned feedback reports to participants. The 4-page report included answers given by the individual GP, the pooled results of the other participants in that country, and an update on laboratory and clinical implications of MA.

Office measurement methods used by participants were divided into (a) albumin/creatinine ratio, reported quantitatively or semiquantitatively, (b) albumin concentration reported as quantitative measurements, and (c) semiquantitative (micro-)albumin test strips.

Clinically important changes in UA results were evaluated using the concept of critical difference (CD). The CD is defined as the minimal difference needed...
between 2 consecutive results to be certain (with a specified level of confidence) that the results are truly different, and that the difference is not due simply to analytical imprecision [coefficient of analytical variation (CVa)] or intraindividual biological variation [coefficient of intraindividual variation (CVi)] (15):

\[
CD = \text{bias} + z \cdot \sqrt{2 \times (CVa^2 + CVi^2)}.
\]

Assuming long-term random bias, e.g., due to calibrations of different reagent lots to be included in the CVa (imprecision under reproducibility conditions), we calculated the CVa for ACR using a CVi of 24% (year-to-year variation) (16) and a z value of 1.64 and 0.84 reflecting 95% and 80% confidence, respectively. We used the calculation of CVa for ACR as an example, since the CVi for this unit category was similar to or lower than the CVi of timed urines or concentrations (see online Data Supplement).

We used McNemar’s test to evaluate preferences for type of urine specimen; otherwise, we used \(\chi^2\) test for categorical variables and Spearman test for correlations. Statistical analyses were performed with SPSS version 14.0, and the significance level was 0.05; 95% CIs are stated in the text when appropriate.

Results

The questionnaire was returned by 2298 GPs, of whom 220 stated no use of UA analysis and were excluded from the study. The response rate varied from 7% to 43% in different countries. An overview of participants is presented in Supplemental Table 1 in the online Data Supplement. Australia and Croatia had to be excluded because they had fewer than 30 responders. The availability of in-office testing ranged from 4% to 88% in different countries. Quantitative ACR or albumin measurements were most commonly used in Norway, Sweden, and Estonia, whereas semiquantitative albumin strips were the most prevalent method used in the other countries (Table 1).

CASE-FINDING FOR MICROALBUMINURIA

For a first-time examination for MA, GPs in all countries except France preferred using morning or random urine samples rather than timed collections (Fig. 1).

Overall, the rate of repeat testing was 62%, ranging from 45% in the Netherlands to 77% in Spain. When a repeat test was requested, the use of random samples was reduced, and significantly more timed samples were used in all countries except France and Hungary, which had a relatively high baseline rate for use of timed sample collection.

Differences in the sample types used for testing were related to in-office equipment. For first-time examination, 95% (95% CI 94%–96%) of GPs with in-office testing and 70% (67%–74%) of GPs without in-office testing used morning or random urine samples. When a large laboratory was used for follow-up tests, the use of timed samples was similar for GPs with or without in-office testing (64% vs 57%). Further, 63% (53%–72%) of semiquantitative strip users, 31% (20%–41%) of quantitative albumin measurement users, and 16% (11%–20%) of ACR users preferred a repeat test to be done in a larger laboratory.

CRITICAL DIFFERENCE

In all countries except the Netherlands, CDs were given for all 4 measurement units (Table 2). The median CDs for an increase or decrease in urinary albumin were similar in most countries (30%–35%); larger changes were stated to be critical for increase of UA in Spain and France and for decrease of UA in Estonia, Spain, and Austria (Table 3). CD did not vary by reporting unit category chosen. Overall, although estimates of in-

<table>
<thead>
<tr>
<th>Country</th>
<th>n</th>
<th>A/C ratio</th>
<th>Quantitative albumin</th>
<th>UA test strips</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>23</td>
<td>3</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Denmark</td>
<td>29</td>
<td>3</td>
<td>3</td>
<td>23</td>
</tr>
<tr>
<td>Estonia</td>
<td>38</td>
<td>3</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Norway</td>
<td>534</td>
<td>342</td>
<td>87</td>
<td>105</td>
</tr>
<tr>
<td>Sweden</td>
<td>91</td>
<td>71</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>France, Hungary, the Netherlands, and Spain</td>
<td>27</td>
<td>0</td>
<td>1</td>
<td>26</td>
</tr>
</tbody>
</table>

* Cobas Integra 400+ (Roche Diagnostics), DCA 2000+ Analyser, and Clinitec semi-quantitative test strip (Siemens AG).
* HemoCue (HemoCue AB), NycoCard Reader (Axis-Shield PoC AS), QuikRead (Orion Diagnostika), and Turbox (Embee Diagnostics).
* Micral-Test (Roche Diagnostics) and MicroAlbustix (Siemens AG).
crease and decrease of urine albumin correlated significantly in most countries, they were not congruent, with a mean $R^2$ of 0.48; ranging from 0.12 (Spain) to 0.63 (France).

Quality specifications for measurement imprecision (CVa) based on the CDs was calculated only for ACR, since the CVi was lowest for this constituent and since the reported CD values were rather similar and independent of the reporting unit category (see Materials and Methods and the online Data Supplement). Median CVa values required to meet the median clinical CD requirements with 80% confidence were similar (about 14%) in most countries for both increase and decrease in ACR values (Table 4). Use of a 95% confidence level resulted in noncalculable CVa values in most cases (see the online Data Supplement).

**Discussion**

Because the study coordinators in each country were asked to send the study material to only 200–600 GPs, the results cannot be considered representative of a

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**Table 2. Units used for measurement of urine albumin as selected by GPs (%) when stating critical differences.**

<table>
<thead>
<tr>
<th>Country</th>
<th>n</th>
<th>mg/mmol creatinine</th>
<th>mg/L</th>
<th>µg/min</th>
<th>mg/24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>77</td>
<td>13</td>
<td>56</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>Denmark</td>
<td>64</td>
<td>52</td>
<td>25</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Estonia</td>
<td>77</td>
<td>36</td>
<td>38</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>France</td>
<td>99</td>
<td>9</td>
<td>17</td>
<td>10</td>
<td>64</td>
</tr>
<tr>
<td>Hungary</td>
<td>34</td>
<td>15</td>
<td>47</td>
<td>6</td>
<td>32</td>
</tr>
<tr>
<td>Netherlands</td>
<td>63</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Norway</td>
<td>1140</td>
<td>49</td>
<td>35</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Spain</td>
<td>130</td>
<td>33</td>
<td>24</td>
<td>4</td>
<td>39</td>
</tr>
<tr>
<td>Sweden</td>
<td>149</td>
<td>54</td>
<td>34</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

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**Fig. 1.** Urine specimen used for first (1. test) and repeat (2. test) UA test. The number of participants is denoted in parentheses.
country. Taken in aggregate, however, the results demonstrate that there is variation among GPs both within and between countries in how they request and interpret UA, and that the recommendations in guidelines are, to a large extent, not followed.

The response rate in this study was rather low, but similar to that observed in other studies of GP practices (10, 17–20). In Croatia, UA testing in the primary health care units has just started (information provided by Croatian colleagues), and understandably the response rate was very low. Australia was the only country that chose to include the questionnaire in a regular newsletter, which may explain the low response rate obtained there. Translating the questionnaire may have introduced difficulties in interpreting the questions and affected replies. However, the questionnaire was pilot tested and reviewed by all country coordinators, and Web-based routines for submission of responses were established. Responses of the GPs in different countries showed a similar pattern, indicating that the results were likely representative of current practice.

The results from this study are discussed in relation to 4 internationally recognized guidelines, those of the International Diabetes Federation (IDF) (6), the American Diabetes Association (ADA) (5), the Scottish Intercollegiate Guidelines Network (SIGN) (4), and the National Institute for Health and Clinical Excellence (NICE) (7). These guidelines recommend that the first test for UA should be a morning or random sample (4–7), probably for reasons of practicability. The results showed nonconformity with this recommendation, especially in France and Hungary, where a timed urine sample was requested by 80% and 35% of participants.
the GPs, respectively. This nonconformity may be explained by local recommendations, e.g., in France (12, 21).

All guidelines recommend, if the first test is positive, 1 (4) or 2 repeat tests (5–7). This recommendation is intended to decrease the influence of the intra-individual biological variation as well as the analytical imprecision on the interpretation of results, and also to exclude interfering factors such as exercise and fever that may cause increase in UA for reasons other than renal disease. It was therefore surprising that from 23% (Spain) to 55% (the Netherlands) of GPs reported making the diagnosis of MA using only 1 test result. These percentages may be underestimates, since participants may be prone to reporting the performance of more actions in a questionnaire than they actually perform in everyday practice (22). It is also noteworthy that many GPs considered changes within the interval for MA (3–30 mg/mmol) as clinically important, when in fact such changes are of little consequence, as both end points of this interval represent MA when put in the context of reference limits or action limits (4–7). Therefore, to the extent that it is recommended that second samples should be obtained to confirm a patient’s degree of abnormal proteinuria, more education of clinicians, and better strategies to implement the practice, are needed.

Availability of in-office testing clearly increased the use of spot (morning and random) samples compared with timed collections. Spot samples are easy to obtain and are in accordance with guideline recommendations. Timed samples were used extensively, however, and especially when repeat tests were performed, indicating that GPs assume these samples to be more reliable. It is reassuring that a majority of semi-quantitative test strip users chose to confirm a positive result with a quantitative measurement. The guidelines are not specific when recommending the type of specimen for a repeat test, but it would be sensible to use a repeat test with a low biological variation such as the ACR. Point-of-care instruments with procedures for ACR measurement have shown “hospital-level” analytical quality (23–26), and a repeat test can therefore be performed in the office laboratory as reported by 84% of GPs who used ACR equipment in their offices.

There are no uniform recommendations in the guidelines on which of the different measurement procedures for UA should be used. This lack of uniformity is reflected in the responses of the GPs where all 4 alternatives were reported (Table 2). It is obvious that different sample types, measurements, and consequently, reporting units can cause misinterpretation and confusion. Professional societies should provide clear guidance on what samples and units of expressions should be used for detecting UA.

Information on critical differences may be important in assessing progression of disease or monitoring effects of therapeutic interventions. Estimation of clinically important differences between consecutive results, reflected in CDs, had a large range among GPs. However, the CDs stated were surprisingly similar regardless of the method of UA analysis. This finding may indicate that some GPs believe small changes to be important, whereas others neglect smaller changes and do not act until changes are rather large. It is not surprising to observe a range of responses, since data on intraindividual biological variation of UA is limited, and CD values are not provided in guidelines (4–7, 27).

The intraindividual variations reported for samples and measurements were in general too large to permit mathematical calculation of CVa with 95% confidence for all measurement procedures (see the online Data Supplement). For ACR, a median CVa of about 14% (Table 4) was calculated from the median CD, using 80% confidence. This CVa should be achievable in primary care (23–26).

In conclusion, our findings suggest that methods for sample collection and results reporting for UA analysis should be as simple as possible to promote uniform practice among GPs. In addition, the need for repeat analyses to diagnose MA may be difficult to incorporate into everyday practice, and the evidence for this recommendation should be weighed against the practicability. The more UA analysis is emphasized in clinical care, e.g., in estimating cardiovascular risk and preventing renal disease, the more guidelines should be concerned with recommendations on laboratory aspects of UA measurement.

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References