Screening for microalbuminuria in patients with type 2 diabetes is incomplete in general practice

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ABSTRACT

INTRODUCTION: National Danish guidelines recommend screening for microalbuminuria with assessment of urinary albumin/creatinine ratio at least annually in patients with type 2 diabetes. To which extent such screening is actually performed is not known.

MATERIAL AND METHODS: A total of 2,057 patients with type 2 diabetes were randomly selected from 64 general practitioners (GPs) from different geographical areas of Denmark. Clinical and laboratory data on the individual patients were collected through the GPs' electronic medical patient records; particular emphasis was given to annual screening for microalbuminuria.

RESULTS: The mean age of the patients was 66.2 ± 11.6 years and 58.7% were male. Only 57.2% of the patients had been screened for microalbuminuria with any method within the preceding 12 months period; of these 76.0% had normo- and 21.0% had microalbuminuria, whereas 3.0% had overt proteinuria. In contrast, 97.6% of patients had had a minimum of one plasma-creatinine measurement within the past year.

CONCLUSION: In Danish primary care, screening for microalbuminuria in type 2 diabetes is insufficiently implemented, whereas renal function is evaluated in almost all patients by plasma-creatinine measurements. The importance of diagnosing microalbuminuria in patients with type 2 diabetes needs to be emphasised.

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The prevalence of chronic kidney disease (CKD) is high in type 2 diabetes [1, 2]. The risk of cardiovascular disease (CVD) is markedly increased when both diabetes and CKD are present [3]. In end-stage kidney disease, 50% of patients die within 4-5 years after initiation of dialysis [4].

Incipient diabetic nephropathy can be detected by the appearance of microalbuminuria [5]. In patients with type 2 diabetes and microalbuminuria, the development of diabetic nephropathy can be prevented or delayed by blood pressure control and medical blockade of the renin-angiotensin system [6]. Moreover, intensified combined multi-pharmacological and lifestyle interventions toward traditional CVD risk factors may reduce renal failure and cardiovascular events by 50% in patients with type 2 diabetes with microalbuminuria [7]. A cost-effectiveness analysis showed that intensive therapy was more cost-effective than conventional treatment from a healthcare payer perspective [8]. It is therefore of major importance to identify patients with type 2 diabetes with microalbuminuria in order to offer optimal protective therapy against renal failure and cardiovascular events.

The Danish national guidelines recommend screening for microalbuminuria by assessment of the urinary albumin/creatinine ratio (UACR) at least annually in patients with type 2 diabetes [9]. In hospital settings, data on the implementation of this screening can be obtained from The National Indicator Project (NIP) [10]. However, there are only limited data on screening for microalbuminuria or CKD in the majority of Danish patients with type 2 diabetes who are followed in primary care settings [11].

The primary purpose of the present study was thus to evaluate the frequency of screening for microalbuminuria, albuminuria and renal function in patients with type 2 diabetes followed in primary care settings in Denmark.

MATERIAL AND METHODS

We aimed at including a minimum of 2,000 patients with type 2 diabetes in the study (corresponding to almost one percent of the total population of patients diagnosed with type 2 diabetes in Denmark).

The inclusion criteria were:

1) Diagnosis of type 2 diabetes
2) Duration of diabetes ≥ 2 years.

The exclusion criteria were:

1) Diabetes managed in secondary care unit
2) Dialysis or history of kidney transplantation
3) Other medical kidney disease (e.g. polycystic kidney disease, glomerulonephritis).

General practitioner selection: Sixty-four general practitioners (GPs) participated in the study. They were ran-

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TABLE 1

Clinical and laboratory characteristics of study participants.

	Screened	Unscreened	Total	p-value[a]
Patients, n	1,176	881	2,057	–
Male/female, %	60.1/39.9	56.9/43.1	58.7/41.3	0.15
Age[b], mean ± SD, years	66.1 ± 11.0	66.3 ± 12.4	66.2 ± 11.6	0.67
Duration of diabetesc, median (IQR), years n	5.0 (3.0-9.0) 1,024	5.0 (3.0-8.0) 736	5.0 (3.0-8.5) 1,760	0.04
Active smokers, %	15.3	16.7	15.9	0.43
Antihyperglycaemic treatment, % treated	89.7	88.1	89.0	0.27
Antihyperglycaemic drugs received[c], median (IQR), n	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.42
Metformin, % treated	70.6	63.5	67.5	< 0.01
Insulin, % treated	12.6	14.0	13.2	0.40
Hypertension, % diagnosed	73.4	66.1	70.2	< 0.01
Antihypertensive treatment, % treated	82.5	75.5	79.5	< 0.01
Antihypertensive drugs received[c], median (IQR), n	2.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	< 0.01
Known cardiovascular disease, %	20.2	19.4	19.9	0.68
Statin, % treated	77.8	66.9	73.1	< 0.01
Acetyl salicylic acid, % treated	49.9	42.4	46.7	< 0.01
Body mass index[b], mean ± SD, kg/m^2 n	30.5 ± 5.5 441	31.3 ± 6.4 212	30.8 ± 5.8 653	0.14
Blood pressure[b], mean ± SD, mmHg				
Systolic n	132.1 ± 13.6 1,116	133.5 ± 16.0 783	132.6 ± 14.6 1,899	0.04
Diastolic n	77.8 ± 8.4 1,116	78.5 ± 9.9 783	78.1 ± 9.0 1,899	0.09
UAE, % normo-/microalbuminuria/proteinuria	76.0/21.0/3.0	–	–	–
P-creatinine, % normal/elevated/severely elevated n	76.0/21.5/2.5 1,164	75.1/22.7/2.1 844	75.6/22.0/2.3 2,008	0.71
Total cholesterol[c], median (IQR), mmol/l n	4.2 (3.7-4.7) 1,163	4.2 (3.7-5.2) 833	4.2 (3.7-4.7) 1,996	< 0.01
LDL cholesterol[c], median (IQR), mmol/l n	2.2 (1.7-2.7) 1,143	2.2 (1.7-2.7) 816	2.2 (1.7-2.7) 1,959	< 0.01
HbA_{1c}[c], median (IQR), % n	6.7 (6.2-7.2) 993	6.7 (6.2-7.2) 729	6.7 (6.2-7.2) 1,722	0.66
GPs, %				
In solo practices	59.8	57.7	58.9	0.36
In big cities	40.6	41.9	41.2	0.60

GP = general practitioner; HbA_{1c} = glycated haemoglobin; IQR = interquartile range; LDL = low-density lipoprotein; P = plasma; SD = standard deviation; UAE = urinary albumin excretion.
a) p-values refer to Student's t test, χ^2-test, Wilcoxon's test, or Fisher's exact test, as appropriate, see "Statistical analyses".
b) Normally distributed variable.
c) Non-normally distributed variable.

domly selected from different geographical regions of Denmark and counted GPs from both solo practices and group settings.

Patient selection: All patients with type 2 diabetes were identified by the GP in collaboration with a specially trained nurse through a search in the individual GP's electronic medical patient records for:

1. Registered diagnosis of diabetes (International Classification of Primary Health Care (IPCP), International Classification of Diseases 10th ed. (ICD10))
2. Present or previous prescription of specific antidiabetic medication (e.g. metformin, insulin)
3. Free text search for the word "diabetes".

From this list, a median of 35 (interquartile range 30-35) patients were randomly chosen. Finally, the selected patients were assigned a log number after which only the GP had access to the data regarding the patients' identity.

The primary end-points were the proportion of patients screened for microalbuminuria within the preceding 12 months and the level of urinary albumin excretion among these patients. The patients' standard clinical and laboratory characteristics were recorded, including age, sex, duration of diabetes, history of CVD and hypertension, smoking, weight, body mass index, blood pressure, pharmacological treatment (glucose-lowering drugs, antihypertensive treatment, anticoagulant medication, lipid-lowering medication), and the following

biochemical variables: glycated haemoglobin (HbA_{1c}), plasma-creatinine, total and low-density lipoprotein cholesterol.

Statistical analyses

Statistical analyses were performed in collaboration with staff at Technical University of Denmark (DTU), where the database is hosted. Patients with a minimum of one analysis of urinary albumin excretion (UAE) (any method) within the preceding 12 month period were classified as "screened", whereas the rest of the patients were classified as "unscreened" for microalbuminuria or proteinuria. Data are presented as mean ± standard deviation (SD, normally distributed parameters) or as median (interquartile range (IQR)). Comparisons between groups were performed with Student's t-test (continuous variables) or χ^2-test with Pearson's correction (discrete variables). For non-normally distributed parameters, Wilcoxon's test or Fisher's exact test were applied. The study was approved by The Danish Data Protection Agency, and the participation of the GPs was approved by the Danish Medical Association.

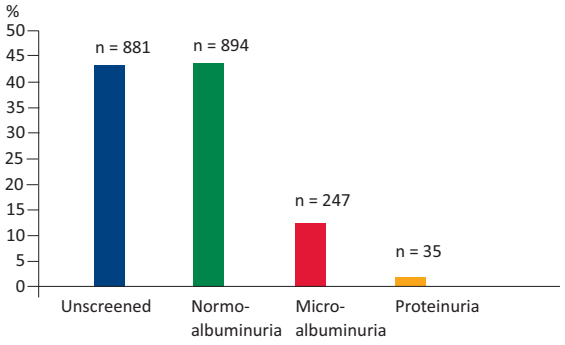
Trial registration: not relevant.

RESULTS

A total of 2,057 patients with type 2 diabetes were included in the study. Their clinical and laboratory characteristics are given in **Table 1**. Their mean age was 66.2 ± 11.6 years, 58.7% were male, and the median diabetes duration was 6.6 (IQR: 3.0-8.5) years.

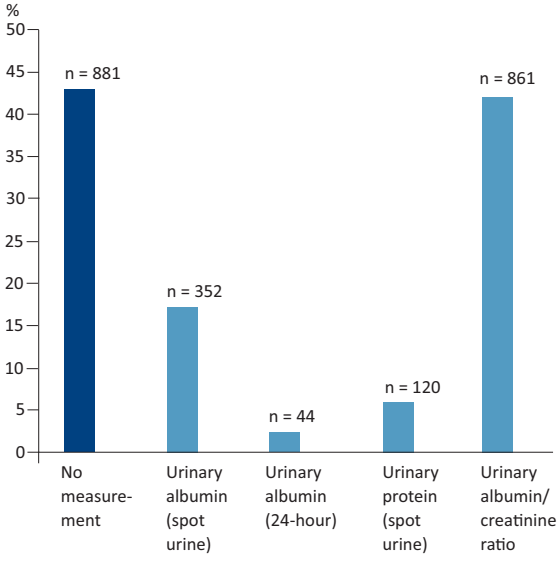
Screening for microalbuminuria: 57.2% of the patients had been screened with a measurement of UAE (any method) within the preceding 12 month period; of these 76.0% had a normal albumin excretion and 21.0% had microalbuminuria, whereas 3.0% had overt proteinuria (**Figure 1**). The method for determining albumin excretion in urine varied: In 41.9%, a minimum of one UACR had been performed, in 2.1% a 24-hour urine sample had been collected, whereas urinary albumin concentration or protein concentration had been measured in a spot urine sample in 17.1% and 5.8%, respectively (**Figure 2**). In a minor proportion of patients, more than one method had been used; for this reason, the total figure slightly exceeds the total of 57.2%. Screened and unscreened patients did not differ with regard to age, sex, duration of diabetes, smoking, antihyperglycaemic treatment, frequency of known CVD, plasma-creatinine, or HbA_{1c}. In contrast, a slightly higher proportion among screened than among unscreened patients was diagnosed with hypertension (73.4 versus 66.1%, respectively, $p < 0.01$); likewise, screened patients were more likely to be treated with acetylsalicylic acid (ASA) and with a statin than unscreened patients

FIGURE 1



Type 2 diabetic patients (n = 2,057) without screening for microalbuminuria ("unscreened") or with normoalbuminuria, microalbuminuria, or proteinuria.

FIGURE 2



Screening methods for urinary albumin excretion in type 2 diabetic patients. In a minor proportion of patients, more than one method had been used; for this reason, the total percentage of screening methods slightly exceeds the total of 57.2% screened patients.

($p < 0.01$ for both comparisons, Table 1). The frequency of screening for microalbuminuria did not differ between GPs in solo versus GPs in group settings or between GPs in cities (> 100,000 inhabitants) with university hospitals versus GPs in smaller towns ($p > 0.3$ for both comparisons, Table 1).

Renal function: 97.6% of the patients had a minimum of one measurement of plasma-creatinine within the past year. Of these, 75.7% had normal plasma-creatinine < 90 micromol/l and only 2.3% had severely elevated plasma-creatinine levels ≥ 150 micromol/l.

DISCUSSION

The main result of the present study was that only 57.2% of the patients with type 2 diabetes in Danish primary care had undergone the recommended screening for microalbuminuria during the preceding 12 month period. Among the screened patients, 21% had micro-

The urinary albumin/creatinine ratio is the recommended analysis for microalbuminuria.

albuminuria and 3% had overt proteinuria. Importantly, renal function had been evaluated by measurement of plasma-creatinine in 97.6% of patients of whom the majority (75.7%) had normal plasma-creatinine level. Only 2.3% had markedly elevated plasma-creatinine levels (≥ 150 micromol/l) indicating moderate to severe renal failure.

Diabetic nephropathy is a common and serious complication in patients with type 2 diabetes. It may lead to end-stage renal failure with a subsequent need for renal replacement therapy [4]. In addition, severe renal failure is associated with a marked risk for CVD. CKD and the associated CVD cause great suffering for the individual patient and these conditions impose an extensive burden on healthcare budgets. Fortunately, many risk factors for the development and progression of diabetic nephropathy [12] and CVD [13] have been identified, and there is now solid evidence that early, targeted pharmacological intervention in the incipient microalbuminuric stage of the disease is highly protective against the development of overt nephropathy [14] and the serious cardiovascular events in this patient group [7, 15]. Screening for the development of microalbuminuria is therefore pivotal in order to identify patients with incipient nephropathy eligible for this intervention. Thus, assessment of the urinary albumin excretion at least annually is recommended in national guidelines on type 2 diabetes [9].

Screening for microalbuminuria and albuminuria can be easily and conveniently conducted with the assessment of UACR in a single urine sample. If the UACR is in the microalbuminuric level of 30-299 mg/g, another two urine samples are needed to establish the presence of microalbuminuria. Furthermore, urinary tract infection has to be ruled out. In case of a markedly increased UACR, a 24-hour urinary sampling is recommended in order to obtain an accurate measure of albuminuria. Determination of the albumin concentration in a spot urine sample is not recommended due to the influence of the urinary volume. In the present study, 41.9% had a minimum of one UACR analysis, whereas a 24-hour urinary sampling had been performed in 2.1%. The inappropriate method with measurement of albumin or protein concentration in a spot urine sample had been used in 17.1% and 5.8%, respectively. Hence, there seems to be uncertainty as to the optimal method when screening for microalbuminuria and albuminuria.

The almost complete monitoring of renal function by blood tests demonstrates a very high awareness of the risk for renal disease in type 2 diabetes. Thus, the rather poor screening rate for microalbuminuria probably reflects a poorer knowledge of the importance and therapeutic consequences of this condition. We found no influence of the GP's solo versus group setting or urbanisation on the screening pattern. Likewise, key clinical and laboratory characteristics were comparable in screened and unscreened patients, which indicates a systematic problem in screening setup as opposed to a deliberate choice of refraining from screening specific patient categories (e.g. very old patients, low-risk patients, etc.).

Møller et al retrospectively examined the records from 97 patients referred from GPs to a secondary care diabetes centre in the 2004-2007 period [10]. The frequency of screening for microalbuminuria in these patients was 53% during the preceding two years. Taking into account that patients in that study were selected by referral to a secondary diabetes centre, which presumably had been preceded by a period of intensified contact to the GP, the screening level was low. Thus, the screening frequency of 57% in a period of only one year in the present much larger group of unselected type 2 diabetic patients might indicate a slight increase in urinary screening frequency during recent years. This hypothesis is supported by another study of 80 patients which reported an even lower microalbuminuria screening rate of only 34% during the two-year period from 2000-2002 [16].

Currently, a new Sentinel Data Capture system is under implementation in Danish primary care [11]. The system will provide individual feedback quality reports for the GP on key data from patients with chronic diseases, including data on screening for complications in patients with diabetes. When this system is fully implemented, presumably within a few years, this will allow for the extraction of data at the national level for research purposes such as the present study, as is the case

for NIP [10]. This new feedback and monitoring modality is likely to improve the screening activity in Danish primary care.

The strengths of the present study obviously rest on the large number of included patients and clinics, allowing for a statistically precise estimate of Danish GPs' true microalbuminuria screening frequency in patients with type 2 diabetes, as well as for statistical analyses of potential factors related to GPs (size of practice, geographical variations) or patients (age, sex, co-morbidity etc.) that could theoretically influence screening habits. Moreover, the primary care based design of the present study with inclusion of different types of GPs (solo/group) from all regions of Denmark strengthens the external validity of the study and minimises the risk of selection bias compared with studies on patients referred to secondary care settings [10]. One potential weakness of the study relates to its reliance on the data quality of the electronic medical patient records of the participating GPs. On the other hand, this problem would truly reflect the "real life" situation for the GP regarding the management of patients with type 2 diabetes, including screening for microalbuminuria, and it therefore does not hamper the external validity of the study.

In conclusion, screening for microalbuminuria in type 2 diabetes in Danish primary care is insufficiently implemented, whereas renal function is evaluated in almost all patients by plasma-creatinine measurements. More information on optimal urinary screening methods and the importance of diagnosing microalbuminuria and albuminuria seems to be needed.

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