Microvascular Complications at Time of Diagnosis of Type 2 Diabetes Are Similar Among Diabetic Patients Detected by Targeted Screening and Patients Newly Diagnosed in General Practice

The Hoorn Screening Study

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OBJECTIVE — To investigate whether screening-detected diabetic patients differ from diabetic patients newly diagnosed in general practice with regard to the presence of microvascular complications.

RESEARCH AND DESIGN METHODS — Diabetic patients, identified by a population-based targeted screening procedure consisting of a screening questionnaire and a fasting capillary whole–blood glucose measurement followed by diagnostic testing, were compared with patients newly diagnosed with diabetes in general practice. Retinopathy was assessed with fundus photography, impaired foot sensitivity was assessed with Semmes-Weinstein monofilaments, and the presence of microalbuminuria was measured by means of the albumin-to-creatinine ratio (ACR).

RESULTS — A total of 195 screening-detected type 2 diabetic patients and 60 patients newly diagnosed in general practice participated in the medical examination. The prevalence of retinopathy was higher in screening-detected type 2 diabetic patients than in patients newly diagnosed in general practice, but not significantly higher. The prevalence of retinopathy was 7.6% (95% CI 4.6–12.4) in screening-detected type 2 diabetic patients and 1.9% (0.3–9.8) in patients newly diagnosed in general practice. The prevalence of impaired foot sensitivity was similar in both groups, 48.1% (40.9–55.3) and 48.3% (36.2–60.7), respectively. The ACR was 0.61 (interquartile range 0.41–1.50) in screening-detected type 2 diabetic patients and 0.99 (0.53–2.49) in patients newly diagnosed in general practice. The difference in prevalence of microalbuminuria was not statistically significant. The prevalence of microalbuminuria was 17.2% (95% CI 12.5–23.2) and 26.7% (17.1–39.0) in screening-detected type 2 diabetic patients and patients newly diagnosed in general practice, respectively.

CONCLUSIONS — Targeted screening for type 2 diabetes (with a screening questionnaire as a first step) resulted in the identification of previously undiagnosed diabetic patients with a considerable prevalence of microvascular complications.

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Type 2 diabetes is a common and serious disease with chronic complications, and it constitutes a substantial burden for both the patient and the health care system. Type 2 diabetes is characterized by an asymptomatic phase between the actual onset of diabetic hyperglycemia and clinical diagnosis. This phase has been estimated to last at least 4–7 years, and consequently 30–50% of type 2 diabetic patients remain undiagnosed (1). Untreated hyperglycemia is an explanation for the relatively high prevalence of retinopathy in newly diagnosed diabetic patients (1,2). Patients in clinical practice are predominantly diagnosed because they have symptoms of hyperglycemia, but screening for type 2 diabetes might make it possible to identify diabetic patients much earlier in the asymptomatic phase. The assumption that early detection and early treatment may prevent or delay the progression of diabetes and its complications has given rise to the recommendations to screen for type 2 diabetes (3,4).

Screening for type 2 diabetes can be carried out in various ways. Targeted screening might be a practical and efficient way of screening because diagnostic testing is then restricted to individuals who are at high risk of having undiagnosed type 2 diabetes. To date, targeted screening studies have focused on the yield of the screening procedure (5,6). To

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Abbreviations: ACR, albumin-to-creatinine ratio; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; SRQ, symptom risk questionnaire; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

our knowledge, no previous studies have reported the prevalence of microvascular complications in diabetic patients identified by targeted screening. It is unclear to what extent these patients differ from newly diagnosed diabetic patients in general practice. With screening one would expect to identify patients earlier in the development of hyperglycemia and with a lower prevalence of complications. In view of these considerations, we compared the prevalence of retinopathy, impaired foot sensitivity, and microalbuminuria at the time of diagnosis in screening-detected patients with the prevalence observed in diabetic patients who were newly diagnosed in general practice. This issue was addressed in a population-based targeted screening program that was based on a screening questionnaire and a fasting capillary whole–blood glucose measurement to select a high-risk population for diagnostic testing (7).

RESEARCH DESIGN AND METHODS

Study population

Diabetic patients detected by screening. The population-based targeted screening procedure was carried out from 1998 to 2000 among the 11,679 inhabitants, aged 50–75 years, of the West Friesland region of the Netherlands, as was previously described in detail (7). In brief, the first step of the screening procedure consisted of the symptom risk questionnaire (SRQ), which was developed in the Hoorn Study to identify people at high risk of having undiagnosed type 2 diabetes (8). The SRQ was validated against the 1999 World Health Organization (WHO) diagnostic criteria of diabetes in a separate random sample of the population of Hoorn. The sensitivity, specificity, and positive and negative predictive values of a SRQ score of 6 are 66, 70, 13, and 97%, respectively (A.M.W.S., unpublished data). The SRQ includes questions about age, sex, BMI, family history of diabetes, use of antihypertensive medication, frequent thirst, shortness of breath, claudication, and use of a bicycle for transportation. It was sent by mail to every person in the targeted screening population. Participants with an SRQ score ≤6 were considered to be at low risk for undiagnosed diabetes and were therefore not invited to participate in any further testing. For individuals with a SRQ score >6, the second step of the screening was a fasting capillary whole–blood glucose measurement. In all individuals with a fasting capillary whole–blood glucose level >5.5 mmol/l, a venous sample was drawn on the same occasion and a 75-g oral glucose tolerance test (OGTT) was performed within 2 weeks. Individuals with a fasting capillary whole–blood glucose >8.5 mmol/l had two fasting plasma glucose (FPG) measurements within 2 weeks. The 1999 WHO diagnostic criteria for diabetes were applied, i.e. FPG ≥7.0 mmol/l on two separate occasions or a plasma glucose level ≥11.1 mmol/l 2 h after the glucose load of the OGTT (9). The total response for the invitation to the screening was 78% and the SRQ calculated for 7,736 participants, after the exclusion of 741 nonparticipants, 417 previously diagnosed diabetic patients, and 275 people missing data or informed consent. A total of 3,301 participants had a SRQ score >6. The response rates for the capillary blood glucose measurement and OGTT were 87 and 89%, respectively. The nonparticipants of the SRQ were significantly younger than participants and more likely to be men. The nonresponders for the OGTT were older than people who did participate. In total, 217 previously undiagnosed diabetic patients were identified in the targeted screening (7).

Diabetic patients newly diagnosed in general practice

All diabetic patients, aged 50–75 years, who were newly diagnosed from 1999 to 2001 in general practice in the towns of Den Helder and Medemblik (situated to the north of the West Friesland region) were invited to participate in the study. For people without symptoms of hyperglycemia, a fasting capillary whole–blood glucose measurement ≥6.1 mmol/l or FPG ≥7.0 mmol/l on two separate occasions were the criteria for diagnosis of diabetes. For individuals with symptoms of hyperglycemia, one fasting capillary whole–blood glucose measurement ≥6.1 mmol/l or one FPG ≥7.0 mmol/l was sufficient for a diagnosis of diabetes, according to the guidelines of the Dutch College of General Practice (10). These diagnostic cutoff points are in accordance with the 1999 WHO diagnostic criteria for FPG. The general practitioners identified a total of 81 newly diagnosed diabetic patients. Of these, 10 were too young to participate in the present study (<50 years of age). As a result, 71 newly diagnosed diabetic patients were eligible and therefore consecutively invited to participate in the study. Ascertainment of referral of all newly diagnosed diabetic patients was not possible because of Dutch privacy legislation.

Individuals with screening-detected type 2 diabetes (SDM) and all diabetic patients who were newly diagnosed in general practice (GPDM) were invited to undergo an extensive medical examination, including assessment of microvascular complications. The screening procedure, diagnostic tests, and physical examination were carried out in a standardized manner by trained PhD students and research assistants at the Diabetes Research Center in Hoorn. All participants gave written informed consent. The ethics committee at Vrije University Medical Center approved the study.

Measurements

Capillary fasting whole–blood glucose levels were obtained with a Hemocue Blood Glucose Analyzer based on the glucose-dehydrogenase method (Hemocue Nederland, Oisterwijk, the Netherlands). Plasma glucose concentrations were assessed by means of a glucose hexokinase method (Roche Diagnostics, Mannheim, Germany). HbA_{1c} was determined by ion-exchange high-performance liquid chromatography with a modular diabetes monitoring system (Bio-Rad, Veenendaal, the Netherlands). Serum total cholesterol, HDL cholesterol, and triglycerides were measured by means of enzymatic techniques (Boehringer-Mannheim, Mannheim, Germany). The Friedewald formula was used to calculate LDL cholesterol, except when the triglyceride level was >4.5 mmol/l. Information about smoking habits, medication use, and educational level was assessed by means of a questionnaire. Weight, height, and hip and waist circumferences were measured with subjects barefoot and wearing only light clothes. Overweight was defined as BMI ≥25 kg/m^2 (11). Blood pressure was calculated as the mean of two measurements performed in a sitting position after 5 min of rest, using a random-zero sphygmomanometer (Hawksley-Gelman, Lancing, Sussex, U.K.). Individuals were considered hypertensive if they had a diastolic blood pressure ≥90 mmHg, had a systolic blood pressure ≥140 mmHg, and/or were taking antihypertensive medication (12).

Microvascular complications

To assess the presence of diabetic retinopathy, fundus photography was carried out following mydriasis of both eyes with tropicamide and phenylephrine eye drops. One photograph was centred on the macula and the other nasally on the optic disc. A 45° CR5 nonmydriatic retinal camera (Canon, Tokyo, Japan) was used, interfaced to a 3CCD Color Video Camera (Sony, Tokyo, Japan). Retinopathy was graded according to the Wisconsin grading system (13) and defined as a Wisconsin grade ≥1.5. The ophthalmologist who carried out the grading of the photographs was blinded to the method of detection of the diabetic patients.

Foot sensitivity was assessed with Semmes-Weinstein monofilaments. The 5.07 (10-g) monofilament was applied to nine sites on each foot. Each site was tested three times in random order, and two or more failures per site to feel the monofilament was regarded as an incorrect answer. Impaired foot sensitivity was considered to be present if one or more incorrect answers were given for either foot (14,15).

The albumin-to-creatinine ratio (ACR) was calculated to determine the presence of microalbuminuria. Urinary albumin was measured by rate nephelometry (Array Protein System; Beckman, Galway, Ireland). Urinary creatinine was measured by means of a modified Jaffé method. Subjects were classified as having (micro)albuminuria if they had an ACR >2.0 mg/mmol (16). In 26 patients in the SDM group and in 5 in the GPDM group, the albumin concentrations were below the detection threshold. These patients were considered not to have microalbuminuria. The prevalence of microalbuminuria was also determined after exclusion of 28 SDM and 10 GPDM who used an ACE inhibitor or an angiotensin II receptor blocker.

Statistical analyses

The characteristics of SDM and GPDM were compared using Student's *t* test for continuous variables, the χ^2 test for dichotomous variables, and the Mann-Whitney *U* test for skewed variables. Fasting plasma glucose, HbA_{1c}, and triglycerides were presented as median and interquartile range because of their skewed distribution. CIs were calculated with the Confidence Interval Analysis software, version 2.0 (17). A *P* value <0.05 was considered statistically significant, based on two-sided tests. SPSS for Windows version 10.1 was used for all analyses.

RESULTS — In total, 195 of the 217 SDM participated in the assessment of microvascular complications. The general practitioners identified a total of 71 newly diagnosed diabetic patients. Of these, eight declined participation in the study and three did not participate in the assessment of microvascular complications. As a result, a total of 195 SDM and 60 GPDM underwent extensive physical examination. Nonparticipants in the examination tended to be older in both groups, but this difference was not statistically significant. There were no significant differences between participants and nonparticipants in the physical examination in either group with respect to sex and glucose levels (data not shown). In the SDM, data were complete for 184, 181, and 192 patients for retinopathy, foot sensitivity, and microalbuminuria, respectively. In the GPDM, data on foot sensitivity and microalbuminuria were complete for all patients, but data on retinopathy were only complete for 54 patients. The absence of photographs, poor quality of photographs, and prevalent eye disease that precluded fundus photography explained the missing data on retinopathy in both groups. Monofilament data were missing for SDM because foot sensitivity was measured during the fifth or sixth visit to the research center; 14 patients did not attend this visit. There were no significant differences between patients with and without missing data on individual microvascular complications (data not shown). No difference was observed in educational level between SDM and GPDM.

Table 1 shows the baseline characteristics of diabetic patients identified by screening and newly diagnosed in general practice. The SDM were slightly, but not significantly, older than GPDM. The GPDM were characterized by significantly higher FPG and HbA_{1c} levels than SDM. HDL cholesterol in the GPDM was lower than in the SDM, and GPDM were significantly less likely to be overweight or have hypertension and more likely to smoke.

Table 2 shows the prevalence of microvascular complications at the time of diagnosis in diabetic patients identified by screening and in general practice. SDM were more likely to have retinopathy, but this difference was not statistically significant. Background retinopathy (Wisconsin grade 1.5) was present in 11 SDM. There were three cases of mild nonproliferative retinopathy (Wisconsin grade 2.0 and 3.0) in the SDM group and one patient with (pre)proliferative retinopathy (Wisconsin grade 4.0) in the GPDM group. The prevalence of impaired foot sensitivity was similar in SDM and GPDM. In both groups, two patients were unable to feel the 10-g monofilament. Although the ACR was significantly higher in GPDM, the prevalence of microalbuminuria was not statistically significantly higher in this group. Macroalbuminuria (ACR >30 mg/mmol) was present in one of the SDM and in three of the GPDM.

CONCLUSIONS — The prevalence of microvascular complications was similar in diabetic patients who were detected by a targeted screening procedure and in newly diagnosed diabetic patients in general practice. This similarity was observed despite the marked difference in glycemic parameters between the two groups.

This is the first study to compare diabetic microvascular complications at the time of diagnosis in patients detected by targeted screening and patients newly diagnosed in general practice. With screening one would expect to identify patients soon after the actual onset of the disease, i.e., earlier in the development of hyperglycemia. One would also expect to identify diabetic patients with a lower prevalence of microvascular complications. However, our findings were not entirely in accordance with these expectations. The glucose and HbA_{1c} levels were indeed lower in SDM compared with GPDM, which might be an indication that SDM were identified earlier in the development of hyperglycemia. In contrast, the prevalence of microvascular complications did not follow a similar pattern. As microvascular complications have been shown to be affected not only by glucose but also by hypertension and other components of the metabolic syndrome (18,19), the targeted screening approach might explain the similarity in prevalence of microvascular complications. The screening questionnaire includes questions on age, sex, BMI, family history of diabetes, use of antihypertensive medication, frequent thirst, shortness of breath, claudication, and use of a bicycle for transportation. Therefore, the tar-

Table 1—*Characteristics of diabetic patients identified by screening and in general practice*

	SDM	GPDM
n	195	60
Age (years)	63.4 ± 7.0	61.4 ± 7.0
Sex (M/F) (% male)	101/94 (51.8)	30/30 (50)
Symptoms at diagnosis (%)	—	76.0
FPG (mmol/l)	7.9 (7.3–9.0)	9.0 (7.7–10.4)*
HbA_{1c} (%)	6.3 (5.8–7.1)	8.3 (7.4–11.0)*
Cholesterol (mmol/l)	5.7 (1.1)	5.5 (1.0)
HDL cholesterol (mmol/l)	1.3 (0.4)	1.1 (0.3)*
LDL cholesterol (mmol/l)	3.57 (0.96)	3.50 (0.96)
Triglycerides (mmol/l)	1.7 (1.2–2.4)	1.8 (1.4–2.3)
Lipid-lowering medication (%)	20.0	16.7
BMI (kg/m^2)	29.8 ± 5.3	29.4 ± 5.8
Overweight (%)	88.7	74.6*
Waist-to-hip ratio		
Men	1.01 ± 0.06	1.00 ± 0.07
Women	0.92 ± 0.08	0.92 ± 0.07
Current smoker (%)	15.4	31.7*
Systolic blood pressure (mmHg)	141 ± 18	141 ± 22
Diastolic blood pressure (mmHg)	86 ± 10	84 ± 12
Antihypertensive medication (%)	45.1	36.7
Hypertension (%)	75.4	58.3*

Data are mean ± SD or median (interquartile range). Overweight was defined as BMI ≥25 kg/m^2, hypertension as diastolic blood pressure ≥90 mm Hg and/or systolic blood pressure ≥140mm Hg and/or use of antihypertensive medication. *Significantly different from SDM.

geted screening procedure identifies diabetic patients with a high prevalence of hypertension, obesity, and lipid abnormalities (7), which in turn might partly explain the relatively high prevalence of microvascular complications in this group.

The difference in diagnostic strategy between the SDM and the GPDM did not influence the microvascular findings. In the screening-detected type 2 diabetic group, the diagnosis of diabetes was based on two elevated FPG values or one elevated 2-h value of the OGTT. In contrast, GPDM were diagnosed on the basis of elevated FPG values only. However, the diagnostic FPG value and the 2-h plasma glucose values have been shown to be equivalent in the diagnosis of diabetes and the association with microvascular complications (9,20,21). Consequently, it seems unlikely that the difference in diagnosis would explain any (lack of) differences in microvascular complications between SDM and GPDM. Misclassification of microvascular complications is another unlikely explanation for our findings because retinopathy, impaired foot sensitivity, and microalbuminuria were assessed and graded according to methods that are widely used and have been internationally validated (13,14,16).

The relatively small sample size of the SDM and GPDM groups and the small number of patients with complications are limitations of this cross-sectional study. The similarity in the prevalence of complications between SDM and GPDM might be partly due to chance due to the limited power. If the number of GPDM had been higher, the difference in microalbuminuria might have become statistically significant. However, the inconsistent differences in prevalence in retinopathy and foot insensitivity between the two groups are not likely to be affected by a higher number of GPDM.

It seems unlikely that nonresponse bias has influenced the estimated prevalence of microvascular complications because the age difference between participants and nonparticipants in the physical examination was not significant and was present in both groups. SDM and GPDM patients did not differ in educational level, and it therefore seems unlikely that a concomitant difference in degree of disease awareness has affected our results. Coverage of care has not influenced the study results because everyone is insured for health care in the Netherlands. As we were unable to ascertain that all newly diagnosed diabetic patients were referred for our study (due to privacy legislation), we cannot exclude that newly diagnosed diabetic patients with more or more severe microvascular complications did not participate in the study.

People with a relatively mild form of a disease, with a slower progression, are more likely to be identified by screening. People with a more progressive type of disease will probably present with symptoms and may be diagnosed in general practice, independent of screening (3, 22). If a lower prevalence of complications is observed in SDM, this could be due to detection early in the development of hyperglycemia, a less progressive form of hyperglycemia, or both phenomena (length time bias). In the present study, the observed higher prevalence of retinopathy and a similar prevalence of impaired foot sensitivity in SDM does not seem to support the presence of length time bias.

Table 2—*Prevalence of microvascular complications at the time of diagnosis in diabetic patients identified by screening and in general practice*

	SDM	GPDM
Diabetic retinopathy (%)	7.6 (4.6–12.4)	1.9 (0.3–9.8)
Impaired foot sensitivity (%)	48.1 (40.9–55.3)	48.3 (36.2–60.7)
ACR*	0.61 (0.41–1.50)	0.99 (0.53–2.49)†
Microalbuminuria (%)*	17.2 (12.5–23.2)	26.7 (17.1–39.0)
Microalbuminuria (%)‡	14.5 (10.0–20.7)	26.0 (15.9–39.6)

Data are % (95% CI) or median (interquartile range). Retinopathy was defined as Wisconsin grade ≥1.5, impaired foot sensitivity was defined as ≥1 incorrect answers to the monofilament for either foot, and microalbuminuria was defined as a ACR >2.0 mg/mmol. *ACR and microalbuminuria, subjects with missing samples excluded; †significantly different from SDM; ‡microalbuminuria, subjects with missing samples and subjects on ACE inhibitors excluded.

This study reports a one-time screening effort. Therefore, results may not be generalizable to diabetic patients detected in a population with screening at regular intervals. Differences between these patients would depend on the duration of the screening interval, the progression of glucose intolerance, and the progression of complications in the general population. Since the SRQ selects patients with an adverse cardiovascular risk profile and because microvascular complications may also develop as a result of cardiovascular risk factors (i.e., hypertension), it is possible that even with regular screening patients identified by this targeted screening procedure would present with microvascular complications.

The ultimate goal of screening is to reduce morbidity and mortality of type 2 diabetes. Our study shows that the use of risk factors for type 2 diabetes and cardiovascular risk factors in a screening test for undiagnosed type 2 diabetes might be an efficient way to select a group of undiagnosed diabetic patients who would significantly benefit. If the results of this study were replicated, preventive diabetes care might be redirected toward early identification based on cardiovascular risk factors and risk factors for type 2 diabetes rather than focusing only on glucose screening.

In conclusion, targeted screening for type 2 diabetes resulted in the identification of previously undiagnosed diabetic patients with a considerable prevalence of microvascular complications.

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