Prevalence of Diabetes and Impaired Glucose Tolerance in 64-Year-Old Swedish Women

Experiences of using repeated oral glucose tolerance tests

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OBJECTIVE — The purpose of this study was to describe the prevalence of diabetes and impaired glucose tolerance (IGT) in middle-aged women and to examine the variability and practical use of the oral glucose tolerance test (OGTT) in the screening for IGT and diabetes.

RESEARCH DESIGN AND METHODS — All 64-year-old women living in Göteborg, Sweden, were invited to take part in a screening examination (n = 4,856). Of these, 82% (n = 3,998) responded and 53% (n = 2,595) participated and underwent anthropometric measurements and a 75-g standardized OGTT that was repeated within 2 weeks in those not showing normal glucose tolerance (NGT).

RESULTS — The prevalences of known and new diabetes, IGT at both OGTTs, and impaired fasting glucose were 4.7, 4.8, 14.4, and 6.4%, respectively. Half of the women with diabetes were previously undiagnosed, and 37% of the diagnoses were based on OGTT and diabetes 2-h values at both or one of the two examinations. Women with IGT at both OGTTs, in comparison with those with one impaired and one normal OGTT, had higher BMI, waist girth, and blood pressure. More than 40% of the women showed impaired glucose metabolism.

CONCLUSIONS — Among these women, the prevalence of undetected diabetes was high and repeated OGTTs were needed to identify and not misclassify a considerable proportion of patients. The degree of glucose tolerance impairment and the number of abnormal OGTTs were directly associated with occurrence of components of the metabolic syndrome.

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The prevalence of type 2 diabetes increases with age with a sharp rise from middle age. Diabetes is a strong risk factor for cardiovascular disease (1), particularly among women (2,3). Type 2 diabetes often remains undetected for a long time, and many patients with newly detected diabetes have complications at the time of diagnosis (1,4). Several studies have indicated that the prevalence of undetected diabetes is about 50% of all patients with diabetes (5–7), an observation that underlines the importance of detecting type 2 diabetes as early as possible.

Impaired glucose tolerance (IGT), increased waist-to-hip ratio (WHR), high BMI, hypertension, and a family history of diabetes are major risk factors for the future development of type 2 diabetes among subjects >60 years of age (8–10). Lifestyle modifications or pharmacological treatment may prevent or postpone conversion to diabetes in subjects with IGT, emphasizing the importance of identifying subjects at risk (11,12). The prevalence of IGT among 60-year-old subjects is estimated to be up to 20% (6,7,13).

The definition of diabetes is based on the blood glucose level that is associated with increased risk for diabetes-associated complications (14–16). According to the latest guidelines, fasting glucose values have been harmonized with OGTT values (14,17). However, the OGTT is characterized by a high degree of intraindividual variability and low reproducibility, and there is a paucity of data regarding the consequences of using this test in large-scale screening. Thus, epidemiological studies examining the prevalence of type 2 diabetes and IGT based on OGTTs in European populations are rare, especially studies based on repeated OGTTs (18).

The aim of the present study was to determine the prevalence of diabetes and IGT in the cohort of 64-year-old women in Gothenburg, Sweden, and also to examine the variability and practical use of the OGTT in screening for IGT and diabetes. This study was performed within the framework of an underlying project examining the association between glucose tolerance status and subclinical atherosclerosis.

RESEARCH DESIGN AND METHODS

— All 64-year-old women identified through the County Register in Gothenburg, Sweden, were sent an invitation letter to participate in a screening that took place in 2001–2004 and included women born in 1937–1940. They were asked to complete and return a reply form in which they accepted or did not accept participation in the screening examination. Those who accepted completed a brief questionnaire that was enclosed. Subjects who in the first reply letter reported a recent cancer diagnosis, chronic inflammatory disease, severe mental disorder, other severe illness, or

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Abbreviations: ADA, American Diabetes Association; FBG, fasting blood glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; WHO, World Health Organization; WHR, waist-to-hip ratio.

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

drug addictions were excluded. Women who could not understand Swedish were also excluded. A second letter was sent as a remainder to nonresponding women. An attempt was made to contact a sample of these nonresponders for a telephone interview concerning their medical conditions including diabetes.

Participants were invited to a screening examination including an OGTT. Women with known diabetes who were being treated with oral antidiabetic drugs or insulin were examined without preceding OGTTs, whereas women with diet-treated diabetes and fasting blood glucose (FBG) <7.5 mmol/l were examined with OGTTs.

All participants received both written and oral information before they gave their consent to take part in the survey. The protocol was approved by the Ethics Committee at Sahlgrenska University Hospital.

A 75-g OGTT was performed in the morning (before 11 AM); fasting- and 2-h postload capillary blood glucose values were measured with the glucose oxidase technique. The participants had been asked to fast overnight, to avoid heavy physical activity during the previous day, and to avoid smoking during the morning before the test. Women who reported a current infection had the examination postponed 2 weeks. Women fulfilling the criteria for diabetes or IGT were reexamined within 2 weeks with a repeated OGTT. If FBG was in the diabetic range at the second examination, an OGTT was not performed.

The examinations also included a questionnaire regarding previous diseases, current medication, smoking habits, and heredity for diabetes. Anthropometric measurements were made, and blood pressure and heart rate were recorded. Body weight was measured in light clothing to the nearest 0.1 kg, and height to the nearest 1.0 cm. Waist and hip circumferences were measured according to current guidelines. Blood pressure was measured in the right arm with the patient in the supine position using a cuff of appropriate size after at least 5 min of rest. The mean of two recordings was used.

Definitions

The World Health Organization (WHO) criteria (19) for capillary blood glucose cutoff values were used. Hence, IGT was defined as FBG < 6.1 mmol/l (110 mg/dl) and ≥7.8-<11.1 mmol/l (≥140-<200 mg/dl) 2 h after glucose load measured on two occasions. Diabetes was defined as FBG ≥6.1 (≥110 mg/dl) and/or ≥11.1 mmol/l (≥200 mg/dl) 2 h after glucose load measured on two occasions. Impaired fasting glucose (IFG) was defined as FBG ≥5.6-<6.1 mmol/l (≥100-<110 mg/dl) and <7.8mmol/l (<140 mg/dl) 2 h after glucose load.

In the overall summary of the screening results (Table 1 and Fig. 1), subjects with normal glucose tolerance (NGT) at the first OGTT were defined as NGT, women with IGT at both the first and second examinations were defined as IGT, women fulfilling the criteria for diabetes at the first examination but for IGT at the reexamination or the reverse were also classified as IGT, and women with IGT or diabetes at the first examination and NGT at the second examination were defined as IGT/NGT. Family history of diabetes was defined as having either a parent or a sibling with diabetes.

Statistical analysis

The statistical analysis was carried out using SPSS version 9.0 for Windows. Results are presented as means ± SD for continuous variables and as percentages for categorical variables. The Mann-Whitney *U* test and ANOVA were used for comparisons between groups, and a linear model was used for testing the trend among groups. Pearson's correlation coefficient was calculated, and multiple regression was used to create an algorithm that was based on FBG and waist girth from the first examination to predict FBG at the second examination (FBG at the second examination = 0.52 + 0.832 × FBG at baseline + 0.002 × waist circumference). $P < 0.05$ (two-sided) was regarded as statistically significant.

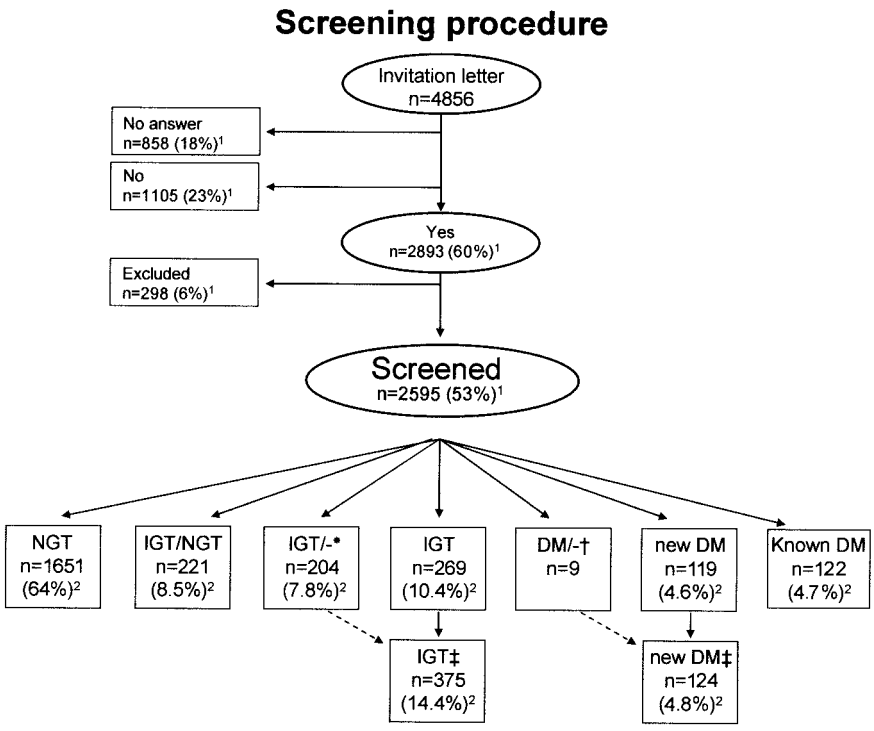

Figure 1—*The screening procedure. [1]Percentage of invited* (n = *4,856). [2]Percentage of screened* (n = *2,595). *IGT at first test; did not participate in a second test. †Diabetes (DM) value at the first test; refused to participate in the reexamination. ‡IGT- and new diabetes–adjusted prevalence rates.*

RESULTS — Of the 4,856 women, 82% responded to the invitation letter and 60% accepted participation in the screening examination (Fig. 1). Six percent were excluded because of the exclusion criteria with the main reason being chronic inflammatory disease. NGT was found in 64% of the 2,595 women who participated in the first screening examination.

The variability in FBG was not related to the duration of fasting before the examinations (mean duration 11.8 h, range 7–20 h). Thus, the quartiles with the longest (13.8 h) and shortest fasting times (10.1 h) did not differ in mean blood glucose values (data not shown).

Table 1—*Characteristics of 64-year-old women by glucose tolerance after two OGTTs*

Variable	NGT	IGT/NGT	IGT	New diabetes	Known diabetes
n	1,651	221	269	119	122
Weight (kg)	70.3 ± 11.3	70.6 ± 11.3	74.8 ± 14.0*	77.5 ± 12.7	80.0 ± 15.2†
Height (cm)	164.5 ± 6.0	164.3 ± 5.6	163.6 ± 5.8*	163.7 ± 6.1	163 ± 5.5†
BMI (kg/m^2)	26.0 ± 4.0	26.1 ± 4.1	27.9 ± 5.0*	28.9 ± 4.4	30.1 ± 5.5†
Waist (cm)	86.6 ± 10.7	87.9 ± 10.9	92.4 ± 12.0*	96.4 ± 11.1	101 ± 13.5†
Hip (cm)	102.8 ± 8.5	102.8 ± 8.4	105.7 ± 10.3*	107.1 ± 9.6	109.3 ± 11.8†
WHR	0.841 ± 0.068	0.854 ± 0.068*	0.874 ± 0.076*	0.900 ± 0.068	0.924 ± 0.072†
Arm (cm)	29.8 ± 3.2	29.5 ± 3.1	30.9 ± 4.0*	31.2 ± 3.8	32.4 ± 4.3†
Neck (cm)	34.7 ± 4.0	35.0 ± 2.3	36.1 ± 2.8*	36.7 ± 2.5	36.9 ± 12.8†
Systolic blood pressure (mmHg)	146 ± 20.2	149 ± 18.9*	154 ± 20.2*	158 ± 20.7	148 ± 21.3†
Diastolic blood pressure (mmHg)	83 ± 9.0	84.0 ± 9.3	86 ± 9.2*	89 ± 9	78 ± 10†
Heart rate (bpm)	70 ± 9	71 ± 10	72 ± 10*	73 ± 11	69 ± 11†
Blood glucose (mmol/l)					
Fasting 1	4.9 ± 0.5	5.1 ± 0.8	5.3 ± 0.7	6.6 ± 1.5	8.8 ± 3.3†
OGTT 1	6.3 ± 0.9	8.6 ± 1.0	9.5 ± 1.6	11.6 ± 2.6†	NA
Fasting 2	NA	4.8 ± 0.5	5.1 ± 0.6	6.5 ± 1.3	8.5 ± 3.0†
OGTT 2	NA	6.8 ± 0.7	9.3 ± 1.1	12.0 ± 2.3†	NA
Family history diabetes	25% (379/1514)	26% (50/195)	34% (84/249)*	48% (53/111)	52% (44/84)†

Data are means ± SD unless otherwise indicated. *$P < 0.05$ compared with NGT; †$P < 0.001$ for trend. NA, not applicable

Diabetes

Known diabetes was found in 122 women (4.7%) and among the remaining women, 250 (9.6%) fulfilled the criteria for diabetes at the first screening examination. At the second screening examination 119 of the 241 women reexamined still fulfilled the criteria for diabetes, whereas 77 showed IGT and 45 women became normal. Nine women fulfilled the criteria for diabetes at the first examination but refused to participate in the repeat examination. In this group an algorithm was used, as described under RESEARCH DESIGN AND METHODS, to calculate a repeat fasting blood glucose value ($R^2 = 0.79$). Five women had a high calculated second FBG result and were defined as diabetic and were included in the final adjusted classification. Hence, the prevalence of diabetes in this survey was 9.5% ($n = 246$) with half of those consisting of newly identified diabetes: 4.8% ($n = 124$).

Diabetes in most of the women (63%) with newly identified disease was diagnosed by two repeated high FBG measurements. However, in 23 of the 119 new patients (19.4%), both OGTTs showed normal FBG values, and the diagnoses were based on two diabetic 2-h tests. A diabetic FBG level at the first test, and a normal FBG but diabetic 2-h value at the second examination were observed in 10 patients. In 11 patients, only the 2-h glucose was in a diabetic range at the first examination with an elevated FBG value at the second examination. Hence, just performing repeated FBG measurements would have resulted in 44 fewer cases, i.e., 37% of all women finally identified as having diabetes using repeated OGTTs. Using FBG values at the first examination and OGTTs at the second would have resulted in 34 fewer patients (29%). Conversely, using an OGTT at the first examination and FBG at the second examination would have resulted in 33 fewer patients (28%).

IGT

At the first screening examination, 22% (571 of 2,595) of the women had IGT. At the reexamination of 367 women with IGT, 175 turned out to have NGT, whereas the remaining 192 women were classified into the IGT group. Of the women with IGT, 21% had a diabetic 2-h postload value on one of the OGTTs. A group of 204 women met the criteria for IGT at the first OGTT but were not reexamined due to technical reasons. Using the same proportion as in the testing of all women with IGT at the first OGTT and who showed IGT at the reexamination, i.e., 52%, we found that 106 of these 204 women were likely to show IGT at the reexamination. Thus, in the final adjusted classification, the prevalence of IGT was 14.4%.

Characteristics by glucose tolerance status

Table 1 shows that with worsening glucose tolerance there was a gradual increase in BMI, waist girth, WHR, and blood pressure, with the exception that known and treated diabetic women had lower blood pressure. The proportion of women with a family history of diabetes was doubled in the diabetic group in comparison with the NGT group. A closer analysis showed that women with IGT/IGT, in contrast to those with IGT/NGT, had higher mean BMI, waist girth, WHR, diastolic blood pressure, and heart rate and that this group contained more subjects with a family history of diabetes than the group with NGT women.

The women, who at the first examination obtained a preliminary diagnosis of diabetes, could after the second examination be classified into three groups: diabetes/NGT, diabetes/IGT, and new diabetes. As shown in Table 2 there was a parallel increase in BMI, WHR, and waist circumference, but no differences in blood pressure, apart from lower values in the known diabetes group. A closer analysis showed that women with diabetes/diabetes, in contrast to those with diabetes/IGT had higher mean BMI, waist girth, and WHR than did the diabetes/NGT group.

The International Diabetes Federation has recently proposed a new definition of the metabolic syndrome with central obesity (waist ≥80 cm) as the obligatory criterion. The proportion of women fulfilling this criterion was high and gradually increased by the degree of impairment of glucose tolerance if both

Table 2—*Characteristics of 64-year-old women by glucose tolerance at two examinations with a preliminary diabetes diagnosis at the first examination*

Variable	Diabetes/NGT	Diabetes/IGT	New diabetes	Known diabetes
n	45	77	119	122
Fasting hours	11.9 ± 1.2	12.4 ± 1.6	12.1 ± 1.7	9.9 ± 4.6
Heredity	52% (22/42)	47% (35/74)	48% (53/111)	52% (44/84)
Weight (kg)	70.9 ± 9.9	73.8 ± 14.9	77.5 ± 12.7†	80.0 ± 15.2
Height (cm)	165.2 ± 5.8	164.0 ± 6.2	163.7 ± 6.1	163 ± 5.5
BMI (kg/m^2)	26.0 ± 3.1	27.4 ± 5.0	28.9 ± 4.4†	30.1 ± 5.5
Waist (cm)	88.1 ± 8.5	90.8 ± 12.0	96.4 ± 11.1†	101 ± 13.5
Hip (cm)	101.3 ± 6.4	104.7 ± 9.6*	107.1 ± 9.6†	109.3 ± 11.8
WHR	0.87 ± 0.06	0.87 ± 0.07	0.90 ± 0.07†	0.92 ± 0.07
Systolic blood pressure (mmHg)	153 ± 20.9	156 ± 22.2	158 ± 20.7	148 ± 21.3
Diastolic blood pressure (mmHg)	84 ± 7.9	86 ± 9.2	89 ± 9.1	78 ± 10.1
Heart rate (bpm)	70 ± 10	71 ± 10	73 ± 11	69 ± 11

Data are means ± SD unless otherwise indicated. *$P < 0.05$, diabetes/IGT compared with diabetes/NGT; †$P < 0.05$, new diabetes compared with diabetes/IGT.

examinations were combined (NGT 73%, IGT/NGT 76%, IGT/IGT 88%, and new diabetes 95%).

In the NGT group 166 women (6.4%) had IFG (FBG ≥5.6–6.0 mmol/l). All together, after passing screening with two OGTTs, 43% of the women had impaired glucose metabolism (diabetes, IGT, IGT/NGT, or IFG).

An FBG ≥5.6 mmol/l had sensitivity (0.87) and specificity (0.84) to identify women with diabetes. Of 2,475 women without known diabetes, 472 had FBG ≥5.6 mmol/l. Performing repeated OGTTs in just this group (472 instead of 2,475) resulted in identification of 103 new cases of diabetes. Sixteen women with new diabetes were not identified with such an approach. The new American Diabetes Association (ADA) criterion of IFG (corresponding to FBG ≥5.0 mmol/l) had higher sensitivity (0.92) but considerably lower specificity (0.52) for identifying new diabetes. A repeated OGTT in just the 1,236 women with FBG ≥5.0 mmol/l resulted in 109 new cases of diabetes. Ten women with newly diagnosed diabetes were not identified with this procedure. Hence, in comparison to the WHO criterion, use of the ADA criterion identified six additional cases of diabetes, but at the cost of 764 more OGTTs.

Nonparticipants

To explore the potential differences between participants and nonparticipants, attempts were made to contact the first 191 women who did not answer the two invitation letters. It was possible to interview 89 women by telephone contact. Three of these women had known diabetes (3.4%) corresponding to 4.7% among the screened patients.

CONCLUSIONS — In the present study a cohort of 64-year-old Swedish women were screened with OGTTs. The results showed that repeated OGTTs seem to be needed to identify all women with diabetes according to the current WHO definition in a middle-aged population. Otherwise, more than one-third (37%) would have remained unidentified if FBG measurements only were used, compared with use of OGTTs at both examinations. Furthermore, the results of the OGTT showed considerable variability as >40% of the women with an OGTT result indicating diabetes at the first examination did not fulfill this criterion at the second examination. In addition, >20% had IGT at the first examination, but in almost 50% of the women there was normalization at the second examination. Finally, there was a continuous relationship between worsening degrees of glucose tolerance and BMI, waist circumference, and blood pressure, with the exception of blood pressure in women with known and treated diabetes. Hence, women with IGT/IGT differed from those with IGT/NGT. More than 40% of the women showed some impairment of glucose metabolism.

In the present study the prevalences of diabetes and IGT were 14 and 22%, if only the first screening examination were used. These results are similar to the results of a Danish and a German study, showing corresponding prevalences of diabetes (12 and 17%) (6,7), whereas the prevalence of IGT seemed to be lower (17%). To the best of our knowledge there has been no previously published study of the prevalence of diabetes and IGT in a cohort of middle-aged women, based on repeated OGTTs and the current definitions of these conditions. Using this approach, we observed a 9.5% prevalence of diabetes in 64-year-old women, whereas the prevalence of IGT was 14.4%. Similar to previous studies, we found that about half of the women with diabetes were newly diagnosed. Taken together, these studies emphasize the need for better strategies to identify subjects with diabetes.

It has been difficult to find simple and generally applicable methods for screening to identify diabetes (20). FBG ≥5.6 mmol/l seems to be the most reliable characteristic of subjects who should be targeted for further examinations (21,22). The proposed new ADA criterion for IFG (plasma FBG ≥5.6 mmol/l) seems to have a less favorable cost/benefit balance (23).

A well-known problem with the OGTT is the high variability in results (20,24), which we also observed in the present study. However, it was also clearly shown in our study that if subjects fulfill the criteria for IGT or diabetes at one OGTT and then show NGT at a repeated test, such subjects differ from healthy subjects with NGT in several characteristics typical of the metabolic syndrome, i.e., high BMI, increased waist girth, and blood pressure. Thus, a lone abnormal OGTT is a clear indication of increased risk, although this cross-sectional study provides no prospective information.

The variability of OGTT results is related to factors such as duration of fasting, degree of physical activity, smoking, and intercurrent diseases. We tried to control for these factors and obtained no indication that the duration of fasting played any major role in the study. It is also likely that when the participating women re-

ceived the information about their IGT, it affected their lifestyle habits between then and the repeated OGTT. However, the reexamination took place within 1–2 weeks, and as discussed above, there was a gradual increase of risk factors in the metabolic syndrome that paralleled the numbers and degrees of IGT tests. This latter observation indicates that the difference between the first and second OGTT results are not primarily explained by changes in lifestyle habits.

The limitations of the present study are that only 64-year-old women were examined, that the participation rate was limited, and that exclusion criteria were used. The advantage of only studying 64-year-old women is that sex and age factors are kept constant. This category of women is also relevant as a cohort with a relatively high incidence of diabetes and a high relative risk of cardiovascular disease (2,7). The response rate was initially >80%, but >20% refused in the end to participate. However, in the telephone interviews of a number of nonparticipating women we could not obtain any evidence that the nonparticipating women had a higher prevalence of known diabetes. The criteria used in the inclusion of women in the study excluded subjects with severe or inflammatory disease. Hence, the results cannot be generalized to women with such diseases.

In summary, the results of this screening study of 64-year-old women showed that the prevalence of undetected diabetes was high and repeated OGTTs were needed to identify and not misclassify a considerable proportion of cases. The degree of glucose tolerance impairment and the number of abnormal OGTTs were directly associated with the occurrence of components of the metabolic syndrome.

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