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Should we consider performing oral glucose tolerance tests more frequently in postmenopausal women for optimal screening of impaired glucose tolerance?

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Abstract

Objective: To investigate an optimal screening protocol for impaired glucose tolerance (IGT) and type II or non-insulin-dependent diabetes mellitus (DM) by using fasting plasma glucose (FPG) and oral glucose tolerance test (OGTT) in postmenopausal women.

Design: One hundred consecutive postmenopausal women were screened with FPG determination, and then all underwent an OGTT. Basal serum lipid and insulin levels of these women were also determined. Insulin sensitivity was determined by using the homeostasis model assessment. Receiver operating characteristic analysis was performed to determine the efficacy of these variables in detecting women with IGT and DM, and optimal cutoff values were determined.

Results: FPG with a cutoff value of 98 mg/dL had the best combination of sensitivity (71%) and specificity (76%) for the detection of IGT and DM. Combined FPG and body mass index screening (with the optimal cutoff value of 26.5 kg/m^2) improved the sensitivity to 96% but decreased the specificity to 47%. This combined screening protocol detected 94% of the women with IGT and all diabetic women.

Conclusions: Given that IGT and DM are common among postmenopausal women and DM can be prevented by nonpharmacologic interventions in women with IGT, OGTT may be used more frequently among these women. Our data indicate that for optimal screening of non-insulin-dependent DM and IGT, OGTT should be considered in postmenopausal women, especially when risk factors in addition to age are present. This model may detect most of the women with IGT and almost all diabetic women.

Key Words: Screening – Impaired glucose tolerance – Diabetes mellitus – Fasting plasma glucose.

Approximately 14 million people in the USA. have diabetes mellitus.[1] Non-insulin-dependent diabetes mellitus (NIDDM) or type II diabetes accounts for 90% to 95% of all cases of diabetes in the USA.[1–4] Diabetes is the seventh leading cause of death in the USA, contributing to roughly 160,000 deaths each year.[1,3] It is also an important risk factor for other leading causes of death, such as coronary heart disease (CHD) and cerebrovascular disease.[4] Diabetes is the most common cause of polyneuropathy and is responsible for more than 50% of the 120,000 annual nontraumatic amputations in the USA.[5,6] Diabetic nephropathy is now the leading cause of endstage renal disease in the USA and, if current trends continue, will soon account for 50% of all patients with renal failure.[7,8] Diabetes is the leading cause of blindness in adults ages 20 to 74 years and accounts for more than 8,000 new cases of blindness each year.[9] Despite these serious consequences, undiagnosed NIDDM is common, and as many as 50% of the people with the disease, or approximately 8 million individuals in the USA, are undiagnosed.[10]

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Impaired glucose tolerance (IGT) is also a risk factor for cardiovascular disease, and patients with IGT are at increased risk of developing frank diabetes.[11,12] Thus, screening for IGT in high-risk populations may be helpful to reduce the burden of NIDDM and its complications. The rate of undiagnosed diabetes increases with age, and there is a steep rise in the incidence of NIDDM after 45 years of age.[2] Therefore, postmenopausal women who present to the outpatient menopause centers may be an appropriate group for screening and early detection.

The objective of this prospective study was to investigate an optimal screening protocol for IGT and NIDDM by using fasting plasma glucose (FPG) and oral glucose tolerance test (OGTT) in postmenopausal women.

METHODS

One hundred consecutive, symptomatic, postmenopausal women who presented with mostly hot flushes and sleep disturbances to the Menopause Outpatient Clinic, Marmara University School of Medicine, between November 1999 and June 2000, were included in the study. Postmenopausal status was defined as the presence of no natural menses for at least 1 year and a serum follicle-stimulating hormone level of greater than 40 IU/L. The following women were excluded from the study: those who had surgical menopause, diabetes, or any known endocrinologic disease and those taking ERT, HRT, or drugs known to affect carbohydrate or lipid metabolism and OGTT results determined during the 6 months preceding the study.

Medical histories were taken, and all subjects underwent screening mammography and gynecologic examination, including cervical smear. Weight and height were obtained, and body mass index (BMI) (kg/m^2) was calculated. After 3 days on a high-carbohydrate diet (300 g/day) and an overnight fast of 10 h to 12 h, all subjects underwent an OGTT (a load of 75 g glucose in 300 mL water). Venous blood samples were obtained at 0 min for glucose, insulin, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride determinations, and at 30, 60, and 120 min for plasma glucose determination. A glycemic response to the OGTT was defined according to the American Diabetes Association (ADA) criteria from 1997: DM, 0 min $\geq$126 and/or at 120 min $\geq$200 mg/dL; IGT, 0 min <126 and at 120 min 140 mg/dL to 199 mg/dL; impaired fasting glycemia, 0 min $\geq$110 and <126 and at 120 min <140 mg/dL; normal glucose tolerance, 0 min <110 and at 120 min <140 mg/dL.[13]

Insulin sensitivity was determined by using homeostasis model assessment (HOMA) according to the following formula: insulin sensitivity (HOMA value) = fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5.

Assays

Plasma glucose concentrations were measured with the glucose oxidase technique using an auto-analyzer (BM/Hitachi 917, Boehringer Mannheim GmbH, Mannheim, Germany). Serum insulin concentrations were measured by chemiluminescent enzyme immunoassay (Diagnostic Products Corporation, Los Angeles, Calif., USA). Intra-assay and total coefficients of variation for different values of insulin were between 3.8% and 4.8% and 4.2% and 7.6%, respectively. Fasting serum triglyceride, total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol concentrations were determined with the BM/Hitachi 917 auto-analyzer using enzymatic calorimetric assays with intra- and interassay coefficients of variation of less than 10% (Roche Diagnostics Corporation, Indianapolis, Ind., USA).

Statistical analysis

The demographic and hormonal data of the women with IGT and DM and those of women with a normal glycemic response were compared by using analysis of variance with a post hoc Tukey test. Receiver operating characteristic (ROC) analysis was performed to determine the efficacy of different variables in detecting women with IGT and DM. Diagnostic sensitivity and specificity were calculated, and the ROC curve was constructed by plotting the sensitivity against the false-positive rate (1-specificity) of various cutoff values for predicting IGT and DM. Area under the ROC curve (AUC) was calculated for age, BMI, duration since beginning of menopause, FPG, serum insulin and lipid concentrations, and HOMA value. The value with the optimal combination of sensitivity and specificity was chosen as the cutoff value. The ideal screening test is one that approaches or reaches the upper left corner of the graph (100% sensitivity and 100% specificity). The cutoff point for each of the screening tests that has the best combination of sensitivity and specificity is located at the "knee" of the graph and is labeled for each parameter. A test that approximates a coin flip is the diagonal from the lower left to the upper right corner of the graph, which has an AUC of 0.5. Positive and negative predictive values were also calculated. Statistical analysis was performed by using the software, SPSS,

Release 10.0 (SPSS, Inc, Chicago, Ill., USA). $P < 0.05$ was considered statistically significant.

RESULTS

Seven women (7%) were found to have DM, and 17 women (17%) had IGT. Six (86%) of the diabetic women were diagnosed with FPG alone. Diabetic women were older, more obese, had longer duration of menopause and higher HOMA values than healthy women (Table 1). There was a trend toward increased fasting serum insulin levels in women with IGT and DM, which did not achieve significance ($p = 0.05$; Table 1). FPG, BMI, HOMA value, and serum triglyceride concentration had significantly higher AUC values than a coin test (i.e., 0.5) (Table 2 and Fig. 1). FPG with the cutoff value of 98 mg/dL provided the best combination of sensitivity (71%) and specificity (76%) as well as the best positive (49%) and negative predictive values (89%) as a screening test for predicting IGT and DM in postmenopausal women (Table 2). When a combined FPG and BMI screening was used with the optimal cutoff values of 98 mg/dL and 26.5 kg/m^2, respectively, and OGTT was performed in women with a high FPG (≥98 mg/dL) and/or high BMI (≥26.5 kg/m^2), sensitivity improved to 96%, and specificity decreased to 47%. Positive and negative predictive values for the use of combined FPG and BMI screening in postmenopausal women to detect women with IGT and DM were 37% and 97%, respectively.

Women with an FPG concentration between 98 mg/dL and 125 mg/dL had a higher risk of having IGT or DM than those with a FPG level of <98 mg/dL ($p =$

TABLE 1. *Clinical and biochemical characteristics of the women in the three different groups*

Characteristic	Healthy women ($n = 76$)	Women with IGT ($n = 17$)	Diabetic women ($n = 7$)	p Value
Age (y; 95% CI)	50.21 ± 5.07 (49.1–51.4)	50.47 ± 4.90 (48.0–53.0)	55.57 ± 3.41 (52.4–58.7)[a]	0.027
Duration since menopause (y; 95% CI)	2.84 ± 2.63 (2.2–3.4)	2.29 ± 1.57 (1.5–3.1)	5.57 ± 3.51 (2.3–8.8)[b]	0.016
BMI (kg/m^2; 95% CI)	25.88 ± 2.88 (25.2–26.5)	27.36 ± 2.70 (26.0–28.7)	28.67 ± 3.77 (25.2–32.2)[c]	0.017
Insulin (μU/mL; 95% CI)	11.41 ± 3.80 (10.5–12.3)	13.88 ± 8.00 (9.8–18.0)	14.94 ± 5.48 (9.9–20.0)	0.05
FPG (mg/dL; 95% CI)	90.50 ± 11.45 (87.9–93.1)	100.65 ± 10.49 (95.3–106.0)[d]	159.29 ± 39.29 (123.0–195.6)	<0.001
Triglyceride (mg/dL; 95% CI)	123.07 ± 57.49 (110.0–136.2)	155.53 ± 74.83 (117.1–194.0)	157.00 ± 77.39 (85.4–228.6)	0.082
Total cholesterol (mg/dL; 95% CI)	218.71 ± 43.27 (208.8–228.6)	235.29 ± 44.53 (212.4–258.2)	209.71 ± 26.28 (185.4–234.0)	0.275
HDL cholesterol (mg/dL; 95% CI)	56.14 ± 11.98 (53.4–58.9)	53.35 ± 10.03 (48.2–58.5)	47.29 ± 14.84 (33.6–61.0)	0.142
LDL cholesterol (mg/dL; 95% CI)	145.20 ± 41.03 (135.8–154.6)	147.71 ± 37.02 (128.7–166.7)	134.43 ± 35.52 (101.6–167.3)	0.754
HOMA value (95% CI)	2.63 ± 1.06 (2.4–2.9)	3.47 ± 2.10 (2.4–4.5)	5.77 ± 2.34 (3.6–7.9)	≤0.001[e]

IGT, impaired glucose tolerance; CI, confidence interval; BMI, body mass index; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA, homeostasis model assessment.
[a] $p = 0.02$ versus healthy women.
[b] $p = 0.02$ versus healthy women and women with IGT.
[c] $p = 0.04$ versus healthy women.
[d] $p = 0.03$ versus healthy women, $p < 0.001$ for other between-group comparisons for FPG.
[e] For all between-group comparisons for the HOMA value.

TABLE 2. *Results of the ROC analysis for different parameters*

Parameter	AUC ± SE	p[a]	95% CI	Optimal cutoff	Sn (%)	Sp (%)	PPV (%)	NPV (%)
Age	0.61 ± 0.07	0.11	0.48–0.74	NA	NA	NA	NA	NA
Duration since menopause	0.56 ± 0.07	0.35	0.43–0.70	NA	NA	NA	NA	NA
BMI	0.69 ± 0.06	0.005	0.56–0.80	≥26.5 vs. <26.5	67 (16/24)	66 (50/76)	38 (16/42)	86 (50/58)
Insulin	0.62 ± 0.07	0.09	0.48–0.75	NA	NA	NA	NA	NA
FPG	0.82 ± 0.05	<0.001	0.72–0.91	≥98 vs. <98	71 (17/24)	76 (58/76)	49 (17/35)	89 (58/65)
Triglyceride	0.66 ± 0.07	0.022	0.52–0.79	≥125 vs. <125	67 (16/24)	62 (47/76)	36 (16/45)	85 (47/55)
Total cholesterol	0.57 ± 0.07	0.32	0.44–0.70	NA	NA	NA	NA	NA
HDL cholesterol	0.49 ± 0.07	0.20	0.36–0.62	NA	NA	NA	NA	NA
LDL cholesterol	0.41 ± 0.07	0.93	0.28–0.54	NA	NA	NA	NA	NA
HOMA value	0.74 ± 0.06	<0.001	0.62–0.86	≥2.9 vs. <2.9	67 (16/24)	67 (51/76)	39 (16/41)	86 (51/59)

ROC, receiver operating characteristic; AUC, area under the curve; SE, standard error; CI, confidence interval; NA, Not applicable; Sn, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; BMI, body mass index; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA, homeostasis model assessment.
[a] Significance of the difference from a test that approximates a coin flip is the diagonal from the lower left to the upper right corner of the graph, which has an AUC of 0.5.

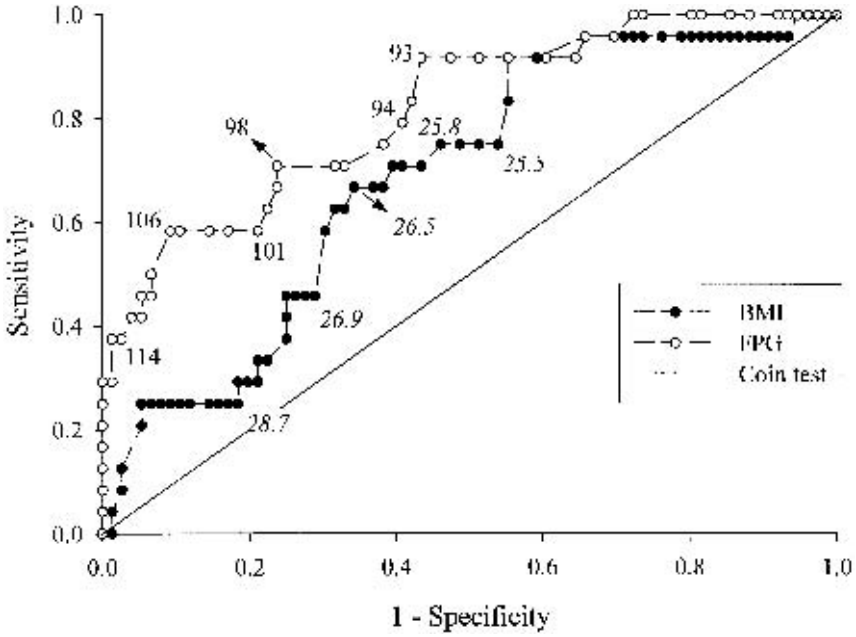

FIG. 1. Receiver operating characteristic (ROC) curves for body mass index (BMI) and fasting plasma glucose (FPG), which have significantly higher area under the curve (AUC) values than a coin test (i.e., a test that approximates a coin flip), which is shown by a diagonal from the lower left to the upper right corner of the graph and also signifies an AUC of 0.5. Numbers on the curves indicate the value of that point, which gives the sensitivity on the *y* axis and 1-specificity on the *x* axis. Arrows indicate the optimal cutoff values, which are the closest points to the left upper corner of the graph.

0.004), and the odds ratio for having IGT or DM was 5.1 (95% confidence interval, 1.7–15.0) in these women. Women who were 54 years of age or older had a higher risk (odds ratio = 6.8; 95% confidence interval, 1.2–37.3) of having DM than those who were younger ($p = 0.02$).

DISCUSSION

The incidence of NIDDM is increasing worldwide, primarily because of increases in the prevalence of a sedentary lifestyle and obesity.[14] Therefore, optimal screening for NIDDM and IGT is valuable. In an attempt to investigate an optimal screening model, we performed OGTT in women presenting to our menopause unit. Our data demonstrate that undiagnosed NIDDM and IGT are common in our cohort of postmenopausal women. The incidence of NIDDM was 7%, and the incidence of IGT was 17%. Wu et al.[15] screened 5,412 women, 38% of whom were postmenopausal. They observed that IGT and DM prevalences in premenopausal women were 3.7% and 3.1%, respectively, whereas the corresponding rates for postmenopausal women were 8.4% and 17.6%, respectively.[15] The relatively low prevalence of IGT in their study can be explained by their use of an older group of postmenopausal women with an average age of 62 years. In addition, they may have missed some of the women with IGT because OGTT was only performed in women who had FPG levels of greater than 99 mg/dL (conversion factor: /18 mmol/L).[15] In the present study, half of the subjects with IGT had FPG levels of less than 99 mg/dL and higher FPG levels were associated with increased risk for both undiagnosed NIDDM and IGT.

In our study, six (86%) of the seven diabetic women were diagnosed with FPG alone. The ADA recommends an FPG determination for diabetes screening, and they suggest an OGTT for individuals with an FPG level of more than 115 mg/dL.[16–18] If this cutoff were applied to our group, two women would undergo OGTT. However, this would not add any diabetic woman to those who were diagnosed with FPG alone and would miss one diabetic woman and all of the women with IGT. In our study group, performing OGTT to postmenopausal women with an FPG level of 98 mg/dL or higher would detect women with IGT and DM with a sensitivity of 71% and specificity of 76%. This would necessitate an OGTT in 35% of our population and would detect 59% of the women with IGT and all of the diabetic women. Combining FPG and BMI with the optimal cutoff levels of 98 mg/dL and 26.5 kg/m^2, respectively, increases the sensitivity. However, this would necessitate an OGTT in 63% of our population and does not seem to be cost-effective because of decreasing specificity. Nevertheless, larger studies from different populations will improve not only the evaluation of considering BMI for screening with OGTT but also the optimal cutoff levels. Our results confirm the ADA's suggestion of screening asymptomatic obese individuals for diabetes.[17,18] The

current data show that obese, postmenopausal women with an FPG level between 98 mg/dL and 125 mg/dL have a fivefold higher risk of having IGT or DM than those with a FPG level of less than 98 mg/dL.

Regarding the population to be screened, it may not be effective to screen all women because it is unknown whether the additional years of treatment that might be received by individuals diagnosed through screening would result in clinically important improvements in diabetes-related outcomes. It has been suggested that it is more effective to screen young adults for NIDDM, contrary to the current recommendations of the ADA to screen only people aged 45 years or older.[19] It has been suggested that the sooner it is detected, the greater the benefits of treatment, because the opportunity to reduce the development of major complications is enhanced.[19] The same principle may be hypothesized for the detection of IGT. Because IGT is an intermediate category between normal glucose tolerance and overt diabetes, and the reported cumulative incidence of diabetes at 10 years varies from 15% to 61%, detection of women with IGT may be helpful to prevent NIDDM by appropriate and inexpensive interventions.[11,20,21] It has been shown that NIDDM can be prevented by changes in lifestyles (i.e., diet and physical activity) of women with IGT.[14,22,23] Because IGT can be identified only by an OGTT but not with an FPG determination alone, performing OGTT more frequently should be considered to detect women with IGT, and a targeted screening may be more appropriate.

As women age, they are more likely to develop IGT and NIDDM.[24] At 50 to 59 years of age, approximately 12% of women have NIDDM; at age 60 years and older, this rate increases to 17% to 18% (a 25%–30% increase).[24] Our data show that women who are 54 years of age or older have a six- to sevenfold higher risk of having DM than those who are younger. Thus, women who present to the outpatient menopause units may be an appropriate group for screening.

An effective screening may also help to reduce the CHD incidence among postmenopausal women by preventing NIDDM. Postmenopausal women who have NIDDM have a substantially higher risk for developing cardiovascular disease, which is a risk that increases after menopause.[24] A postmenopausal woman who has DM is three times more likely to develop CHD or stroke than a woman who does not have DM.[24] Limited number of subjects is the weakness of the present study. Although long-term studies with larger groups from different populations should be performed to analyze the effectiveness of a screening program combined with the appropriate interventions for patients who are found to have IGT, it seems that performing an OGTT should be considered in postmenopausal women, especially when risk factors in addition to age are present.

CONCLUSIONS

Given that IGT and DM are common among postmenopausal women and DM can be prevented by nonpharmacologic interventions in women with IGT, OGTT may be performed more frequently among women who present to menopause units. According to our data, it seems that postmenopausal women with a BMI of 26.5 kg/m^2 or higher and/or an FPG of 98 mg/dL or higher are an appropriate target group to suggest an OGTT. This model may detect most of the women with IGT and almost all diabetic women. However, future studies with larger groups in different populations will effectively demonstrate the cost-effectiveness of targeted screening of postmenopausal women for IGT.

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