Sensory Function and Albumin Excretion According to Diagnostic Criteria for Diabetes

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OBJECTIVE — The purpose of this study was to examine sensory function and albumin excretion according to categories of glucose tolerance in individuals undergoing screening for diabetes.

RESEARCH DESIGN AND METHODS — Sensory function and albumin excretion measurements were obtained in 636 individuals at the time of screening for diabetes according to American Diabetes Association glucose tolerance criteria. Sensory thresholds were measured by forced-choice techniques. Albumin-to-creatinine ratios were calculated from spot urine samples.

RESULTS — Of 90 individuals whose glucose levels were in the range for diabetes, 65 had fasting glucose values \(\geq 126\) mg/dl, whereas 25 had 2-h glucose values \(\geq 200\) mg/dl, with fasting glucose values \(<126\) mg/dl. In covariance analyses, those with fasting glucose levels \(\geq 126\) mg/dl had higher vibration (\(P < 0.01\)) and thermal (\(P < 0.05\) for cool and warm) thresholds than those with normal glucose tolerance. This pattern was also evident for albumin-to-creatinine ratios (\(P < 0.001\)). In contrast, those with 2-h glucose values \(\geq 200\) mg/dl and fasting glucose values \(<126\) mg/dl had sensory threshold and albumin-to-creatinine ratio values similar to those of the normal group. Individuals with fasting glucose levels \(\geq 126\) mg/dl had higher vibration threshold and albumin-to-creatinine ratio values (\(<0.05\) and \(<0.01\), respectively) than those with levels \(<126\) mg/dl.

CONCLUSIONS — Sensory threshold and albumin excretion values already tend to be greater than normal at screening in individuals with fasting glucose levels \(\geq 126\) mg/dl, but not in those with levels \(<126\) mg/dl. A reliance on fasting glucose levels \(\geq 126\) mg/dl for screening might not be sufficient for early intervention and the optimal prevention of diabetes complications.

The criteria for type 2 diabetes have essentially been based on the degree of hyperglycemia. In 1979, the National Diabetes Data Group recommended that fasting glucose levels \(\geq 140\) mg/dl or 2-h glucose levels \(\geq 200\) mg/dl should be used as criteria for diabetes (2). More recently, the American Diabetes Association (ADA) has recommended that the fasting glucose criterion be lowered to \(\geq 126\) mg/dl (3). Although the rationale for this modification was based on several factors, a major consideration was the low frequency of retinopathy in individuals whose fasting glucose levels were \(<126\) mg/dl.

There is less information available with regard to glucose thresholds for other complications of diabetes. Data are particularly sparse regarding the prevalence of these complications at the time of diagnosis of type 2 diabetes, especially according to different diagnostic criteria that are used. In this report, data are presented from 636 individuals who had assessments of sensory function and albuminuria at the time they were screened for type 2 diabetes with oral glucose tolerance tests (OGTTs).

RESEARCH DESIGN AND METHODS — The 636 study participants were recruited through community notices of screening for diabetes. Individuals 25–60 years of age were invited to participate in a research project that involved screening for diabetes. Those with a history of glucose intolerance or on medication that could influence oral glucose tolerance testing were excluded. All participants resided in Miami-Dade or Broward counties in South Florida. This study was approved by the Medical Sciences Subcommittee for the Protection of Human Subjects at the University of Miami, and all participants provided signed informed consent.

As previously described (4), participants were seen after a 12-h overnight fast. All historical information was obtained by interview. For the OGTT, after
a sample for fasting blood glucose and HbA1c was obtained, 75 g carbohydrate was ingested. Blood samples for glucose determinations were then collected at 30-min intervals for 2 h. Glucose measurements were performed with a Beckman analyzer (Beckman, Fullerton, CA). ADA criteria from 1997 were used to classify subjects into three categories: normal, impaired glucose tolerance (IGT) (2-h glucose ≥140 to <200 mg/dl), and diabetes (fasting glucose ≥126 mg/dl and/or 2-h glucose ≥200 mg/dl) (3). Those with impaired fasting glucose (≥110 to <126 mg/dl) were included in the IGT category. HbA1c was measured initially by cation-exchange chromatography; however, the assay was changed to high-performance liquid chromatography during the study. HbA1c was measured by the latter method in 58% of the participants. A urine sample was obtained during the clinic visit for measurement of albumin and creatinine. An enzyme-linked immunosorbent assay produced by Exocell (Philadelphia, PA) was used to measure urine albumin. Urine creatinine was measured by a colorimetric method on the COBAS MIRA using Roche reagents.

Quantitative sensory assessments were obtained as participants were undergoing the OGTT. They were performed by three individuals and included measurements of vibration, warm, and cool perception thresholds at the right hallux and the vibration perception threshold at the right index finger according to standard procedures (see below). The sensory tests were completed before knowledge of the results of the OGTT.

Warm and cool thresholds were determined with the Thermal Sensitivity Tester (Sensortek, Clifton, NJ) by testing the ability of patients to discriminate temperature differences from 25°C. For measurements of warm sensitivity, one plate was set at 25°C and the other plate was set at a higher temperature. The two plates were changed according to a standard algorithm. The right hallux was placed on each of the two plates for ≥2 s, and subjects were asked which plate was warmer. Participants were first asked to discriminate a temperature difference of 10°C. If there was an incorrect response, they were tested again at the same level and the difference was not lowered until there were two correct responses in a row. With a correct response, the temperature difference between the two plates was lowered by 10% decrements until a difference of 1°C was reached. At that point, the difference was gradually lowered by 0.1°C for the remainder of the test. For temperature differences <1°C, it was necessary for subjects to respond correctly twice in a row at the same level before the temperature difference was reduced. The test was concluded after five incorrect responses. The threshold for warm perception was determined by averaging the levels of the five incorrect responses and the levels of the last five correct responses after excluding the highest and lowest values. The cool threshold was measured in the same manner, with one plate set at 25°C and the other plate set at a cooler temperature. Participants were asked which plate was cooler. The absolute temperature differences from 25°C and the algorithm were the same as those for warm threshold testing.

Measurements of vibration perception thresholds were obtained with the Vibratron II (Sensortek, Clifton, NJ). Subjects placed the hallux and index finger on each of two probes for ≥2 s with instruction to avoid placing excessive pressure on the probes. The vibrating probe was alternated according to a standard algorithm, and participants were asked to identify that probe. The amplitude of vibration was set initially at 10 units. This was gradually decreased in a manner similar to that for thermal sensitivity testing until there were five incorrect responses. The thresholds for vibration perception were calculated in an identical fashion to those for thermal perception.

Data analysis

For comparisons between groups, t tests for the comparison of independent means were utilized. Multiple regression analyses were utilized to allow for covariates. Log transformations (base 10) were performed to normalize certain variables. The sensory threshold and albumin excretion values were presented according to the 1997 ADA diagnostic criteria. They were also examined according to the recent recommendation of the ADA to lower the impaired fasting glucose criterion to ≥100 mg/dl instead of ≥110 mg/dl (5). P values are two sided. Calculations were performed with the Systat statistical package.

RESULTS — The characteristics of study participants are shown according to sex in Table 1. Fifty-nine percent of the study participants were women.

The participants are further characterized according to glucose tolerance status in Table 2. Those found to have criteria consistent with type 2 diabetes were subdivided according to whether the fasting glucose was <126 or ≥126 mg/dl. Ninety individuals had criteria consistent with type 2 diabetes. Of these, 65 had fasting glucose levels ≥126 mg/dl (FG≥126 group), whereas 26 had fasting glucose levels <126 mg/dl, but had 2-h glucose levels ≥200 mg/dl (FG<126 group). All but six subjects (9%) with fasting glucose ≥126 mg/dl had 2-h glucose values ≥200 mg/dl.

Those who had criteria for IGT and those in both type 2 diabetes groups were appreciably older and had higher BMI values than those in the normal glucose tolerance (NGT) group. All groups with abnormal glucose tolerance had much higher fasting insulin levels than the NGT group, but the differences were only significant for the IGT and FG≥126 groups (P < 0.001 for both groups). The IGT and FG<126 groups had higher 2-h insulin levels than the NGT group (P < 0.001 for both). When the FG≥126 group was compared with the FG<126 group, the former had significantly higher HbA1c levels and lower 2-h insulin levels (P < 0.001 for both comparisons). The difference in HbA1c levels between these groups remained significant when comparisons were made according to each HbA1c assay (P < 0.01 for both assays). Age and BMI were similar between those groups, however.

Table 3 shows sensory perception threshold and albumin-to-creatinine ratio values according to categories of glucose tolerance. The P values shown are for differences, with allowances for age, height, and sex in covariance analyses. Vibration thresholds at the hallux (P < 0.01) and

Table 1 — Characteristics of participants according to sex

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>374</td>
<td>262</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42.6 ± 10.0</td>
<td>44.9 ± 10.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.0 ± 6.5</td>
<td>27.8 ± 4.4</td>
</tr>
<tr>
<td>White (%)</td>
<td>83</td>
<td>90</td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>76</td>
<td>75</td>
</tr>
</tbody>
</table>

Data are means ± SD for continuous variables.
Complications and criteria for diabetes

Table 2—Characteristics of participants according to glucose tolerance status

<table>
<thead>
<tr>
<th></th>
<th>NGT</th>
<th>IGT</th>
<th>Type 2 diabetes</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fasting glucose</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;126 mg/dl</td>
</tr>
<tr>
<td>n</td>
<td>435</td>
<td>111</td>
<td>25</td>
</tr>
<tr>
<td>Age (years)</td>
<td>41.5±10.2</td>
<td>46.4±9.7*</td>
<td>49.4±7.3*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.1±5.6</td>
<td>29.4±6.2*</td>
<td>29.6±5.2†</td>
</tr>
<tr>
<td>Log fasting insulin</td>
<td>1.88±0.27 (76)</td>
<td>1.99±0.27 (97)*</td>
<td>1.99±0.29 (97)</td>
</tr>
<tr>
<td>(pmol/l)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Log 2-h insulin</td>
<td>2.57±0.36 (367)</td>
<td>2.87±0.34 (746)*</td>
<td>2.93±0.37 (857)*</td>
</tr>
<tr>
<td>(pmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>4.95±0.71</td>
<td>5.37±0.68*</td>
<td>5.73±0.60*</td>
</tr>
</tbody>
</table>

Data are means ± SD and means ± SD (antilog). Twelve subjects in the NGT group and 1 in the FG≥126 group did not have HbA₁c measurements, 3 in the NGT group did not have insulin measurements, and 2 outliers were not included for HbA₁c data in the NGT group. *P<0.01, †P<0.05, for comparisons with the NGT group from covariance analyses; ‡P<0.001, for comparisons with the FG<126 group from covariance analyses.

warm and cool thresholds (P<0.05) were significantly greater in the FG≥126 group than in the NGT group. Vibration thresholds at the hallux were also greater in the FG≥126 group than in the FG<126 group (P<0.05). The FG<126 and NGT groups had similar vibration thresholds. Although cool thresholds were higher in the FG<126 group than in the NGT group in a univariate analysis (P<0.01), the difference was not significant in the covariance analysis. There were no significant differences between the FG≥126 and FG<126 groups for the thermal thresholds.

In covariance analyses with allowances for age, systolic blood pressure, and sex, albumin-to-creatinine ratios were significantly higher in the FG≥126 group than in the NGT group (P<0.001), whereas ratios in the FG<126 group were similar to those in the NGT group. The ratios in FG≥126 subjects were also significantly greater than those in FG<126 subjects (P<0.01). The proportion of those with ratios ≥30 mg/g was also substantially greater in the FG≥126 group than in the other categories (18 vs. 4% in each of the other categories).

In Table 4, sensory threshold and albumin-to-creatinine ratio values were shown when FG≥126 subjects were subdivided according to whether the fasting glucose value was <175 or ≥175 mg/dl. The values for the NGT group are also shown for comparison. Covariance analyses included the same variables as previously indicated. With the exception of the vibration thresholds at the finger, all of the sensory thresholds were significantly higher in those whose fasting glucose was ≥175 mg/dl than in those in the NGT group (P<0.01 for all). In those whose fasting glucose was <175 mg/dl, vibration thresholds at the hallux were almost identical to those in the group with fasting glucose ≥175 mg/dl and significantly higher than those in NGT group (P<0.05). The group with fasting glucose values ≥175 mg/dl also had markedly higher albumin-to-creatinine ratio values than did subjects in the NGT group (P<0.001). Although the values of the group with fasting glucose levels <175 mg/dl were not as high, they were still significantly higher than those of the NGT group (P<0.05).

The data for the sensory thresholds and the albumin-to-creatinine ratios were also examined according to the new ADA criterion for impaired fasting glucose (≥100 to <126 mg/dl) because that had potential bearing on the sensory threshold and albumin excretion values of the NGT and IGT categories. Although the mean sensory and albumin excretion values were virtually identical, the comparisons between the FG≥126 and NGT groups became nonsignificant for the thermal thresholds. This apparently was a function of the markedly reduced number of NGT subjects (435 vs. 369). All other comparisons for the sensory thresholds and albumin-to-creatinine ratios that
had been statistically significant remained so.

**CONCLUSIONS** — The data presented indicate that at screening for type 2 diabetes, individuals with fasting glucose levels ≥126 mg/dl tend to have higher sensory thresholds and greater albumin excretion than those with NGT. In contrast, it appears that individuals with fasting glucose levels <126 mg/dl but with 2-h glucose levels ≥200 mg/dl have sensory threshold and albumin excretion values that do not differ from those with NGT. Moreover, the direct comparisons between these two hyperglycemic groups suggest that those with fasting glucose values ≥126 mg/dl have higher vibration thresholds at the hallux and greater albumin excretion.

The much higher HbA1c levels and lower 2-h insulin levels in the FG≥126 group than in the FG<126 group suggest that the former represents a more advanced stage of metabolic progression. Thus, those in the FG≥126 group are likely to have had a longer duration of the hyperglycemic condition. This could explain the pattern of higher sensory thresholds and greater albumin excretion in FG≥126 subjects. However, it is still possible that the FG≥126 and FG<126 groups represent homogeneous disorders rather than different stages of the same disorder.

In an earlier report from this screening study (4), data were provided on sensory function during screening for type 2 diabetes (see below). The much larger number of participants in the present report allows for an assessment of the presence of complications according to criteria for type 2 diabetes. Also, data on albumin excretion are now presented.

<table>
<thead>
<tr>
<th>Table 4—Sensory thresholds and albumin-to-creatinine ratios according to glucose levels when fasting glucose ≥126 mg/dl</th>
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<tbody>
<tr>
<td><strong>n</strong></td>
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<tr>
<td>---</td>
</tr>
<tr>
<td><strong>Vibration (units)</strong></td>
</tr>
<tr>
<td>Hallux</td>
</tr>
<tr>
<td>Finger</td>
</tr>
<tr>
<td>Warm (°C)</td>
</tr>
<tr>
<td>Cool (°C)</td>
</tr>
<tr>
<td>Log albumin-to-creatinine ratio (μg/g)</td>
</tr>
</tbody>
</table>

Data are means ± SD for continuous variables and means ± SD (antilog). *P < 0.05, †P < 0.01, ‡P < 0.001, for comparisons with the NGT group from covariance analyses.

There are few studies that have examined indexes of neuropathy at the time of screening for type 2 diabetes. In our earlier report from this study (4), when fewer participants were accrued, we found that sensory thresholds were increased, but not significantly, in those with National Diabetes Data Group (3) diagnostic criteria for type 2 diabetes. In another study (6), there was some nerve dysfunction evident in individuals who were newly diagnosed through screening. Neuropathic abnormalities were also evident in some other studies of newly diagnosed diabetic patients (7–10). However, we are unaware of any studies that have examined the presence of neuropathic abnormalities at screening for type 2 diabetes according to whether fasting glucose values ≥126 mg/dl or 2-h glucose values ≥200 mg/dl are used as diagnostic criteria.

Data from several studies indicate that excess albuminuria can be present at or soon after diagnosis (11–15). In some individuals, it may even be present before hyperglycemia develops (16). The data in the present study are consistent with another study (15) that showed that soon after the onset of type 2 diabetes there is a relation between the extent of albumin excretion and the severity of type 2 diabetes.

One measurement of the albumin-to-creatinine ratio is not necessarily indicative of renal pathology. An abnormal value could be a transient phenomenon due to a number of factors, even perhaps changes in glucose levels (17). Our data could be consistent with this concept because there was a marked association between albumin excretion and fasting glucose levels. However, it has been hypothesized that increased albumin excretion in itself can contribute to the pathogenesis of nephropathy (18). Thus, whether or not the increased albumin excretion is indicative of renal pathology, its presence may still be meaningful.

There was evidence in FG≥126 subjects that sensory thresholds and albumin excretion are elevated at screening, even when the degree of hyperglycemia is more moderate. Those whose fasting glucose levels were <175 mg/dl had higher vibration threshold values than did those in the NGT group. Although albumin excretion was much greater in FG≥126 subjects when glucose values were relatively higher, those with fasting glucose levels <175 mg/dl still had more albumin excretion than those in the NGT group.

According to the ADA criteria, fasting or 2-h glucose abnormalities must be confirmed before type 2 diabetes can be diagnosed (3). Since findings in this study are based on one glucose measurement, it is possible that some of those with criteria for type 2 diabetes may have been misclassified. It is doubtful, however, that such misclassification would have negated the patterns that were observed.

The number of those who had fasting glucose levels <126 mg/dl with 2-h glucose levels ≥200 mg/dl can be considered relatively small, but the comparisons of that group with others were quite consistent across the end points. It will be interesting to see whether observations for neuropathic, nephropathic, and other end points are similar in future studies.

A rationale for screening is based on evidence that lowering blood glucose levels can help to delay or prevent the development of diabetes complications (19,20). By identifying hyperglycemic individuals through screening, earlier treatment could then be initiated. Based on this concept, the ADA has recommended...
that it is appropriate to screen certain individuals at risk for type 2 diabetes (21). It has advised, however, that screening should generally be restricted to fasting glucose measurements. The common use of oral glucose tolerance testing was not thought to be feasible, although it was considered appropriate for certain individuals. Although the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus has recently discussed the potential advantage of the use of the OGTT for diagnostic purposes (5), the ADA still recommends the fasting glucose for screening (22).

Data presented in this report raise questions about these practice recommendations. The findings of increased sensory thresholds and urinary albumin excretion in individuals with fasting glucose levels ≥126 mg/dl at screening suggest that the ≥126 mg/dl threshold is too high (or perhaps “too late,” given the evidence for the metabolic progression of type 2 diabetes) for the effective prevention of complications. The use of 2-h glucose levels would identify a substantially greater number of individuals earlier in the course of type 2 diabetes, before the appearance of overt complications for most. Of those in this study who had glucose values in the diabetic range, 28% would have been undetected by the use of the fasting glucose criterion alone. Studies of both European and U.S. adults (23,24) have also indicated that an appreciable proportion of individuals remain undiagnosed when only the fasting glucose is obtained.

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus has recently lowered its criterion for impaired fasting glucose to ≥100 mg/dl (5). The additional lowering of the fasting glucose criterion for diabetes might partially obviate the need for 2-h glucose levels. Although this strategy will misclassify some who would not develop persistent hyperglycemia, it could ultimately lead to earlier and more effective interventions. Moreover, such a modification would be consistent with the concept that pathogenetic processes of type 2 diabetes are already occurring well before the advent of marked hyperglycemia.

References