Does Syndrome X Exist in Hypertensive Elderly Persons With Impaired Glycemic Control?

Karen C. Johnson,1 Marshall J. Graney,1 William B. Applegate,1,4 Abbas E. Kitabchi,2 John W. Runyan,1 and Gale H. Rutan1

1Departments of Preventive Medicine, and 2Medicine, 3Memphis VA Medical Center, and 4General Clinical Research Center, the University of Tennessee, Memphis.

Background. This report focuses on the glycemic state in relation to insulin and lipid levels of a cohort of elderly hypertensive persons to estimate the prevalence of syndrome X.

Methods. A cross-sectional study was performed at the University of Tennessee, Memphis, and the General Clinical Research Center (GCRC) on 95 participants in the Trial of Nonpharmacologic Interventions in the Elderly (TONE) study who agreed to participate in an ancillary study. A standard oral glucose tolerance test (OGTT) with insulin and C-peptide levels and a fasting lipid profile were obtained.

Results. In this sample of healthy elderly participants with hypertension who were taking an antihypertensive medication, 43 (45.3%) had normal glucose tolerance (NGT), 41 (43.2%) had impaired glucose tolerance (IGT), and 11 (11.6%) had undiagnosed non-insulin-dependent diabetes mellitus (NIDDM). Fasting hyperinsulinemia occurred in only one participant, who was in the IGT group. Hypertiglyceridemia and low high density lipoprotein (HDL) occurred in four persons, none of whom had hyperinsulinemia. Persons in the NIDDM and IGT groups had decreased beta cell function compared to persons in the NGT group, but did not have increased peripheral insulin resistance as estimated from the OGTT data.

Conclusions. Our data demonstrated that in this cohort of elderly hypertensive participants with a high prevalence of central obesity, impaired glycemic control was common, but was not associated with fasting hyperinsulinemia or peripheral insulin resistance. Furthermore, we conclude that syndrome X essentially did not occur in these participants and postulate that the primary etiology for their impaired glycemic control is beta cell dysfunction. Further research is needed to elucidate these relationships.

Hypertension is a prevalent medical condition occurring in over 43 million adults in the United States (1). Diabetes mellitus is also a common medical disorder, with approximately 6.6% of the U.S. adult population having this condition (2). Further, there is evidence to suggest that hypertension occurs more frequently in persons with glucose intolerance (3–5). Peripheral insulin resistance resulting in hyperinsulinemia has been postulated to be an etiologic mechanism leading to essential hypertension and glucose intolerance (6–13). Peripheral insulin resistance has also been implicated as the underlying cause of syndrome X (12). Syndrome X is a clustering of risk factors including peripheral insulin resistance, glucose intolerance, hyperinsulinemia, hypertension, increased triglycerides, and decreased high density lipoprotein (HDL) which is thought to predispose persons to an increased risk for coronary artery disease (12). However, controversy continues regarding whether hyperinsulinemia/insulin resistance is an independent risk factor for coronary artery disease, especially in elderly persons (14–16).

Given that the prevalence of hypertension and glucose intolerance increases with age, then one may reasonably speculate that the prevalence of syndrome X in elderly persons with hypertension will also be increased (1,2). However, it is unclear from the literature what the prevalence of syndrome X is in elderly persons. To explore this area we conducted an ancillary study of a subset of randomized participants in the Trial of Nonpharmacologic Interventions in the Elderly (TONE) at the University of Tennessee, Memphis, site. This report will focus on the glycemic state in relation to insulin and lipid levels of the TONE ancillary study participants to estimate the prevalence of syndrome X in this elderly hypertensive cohort. We have also estimated beta cell function and peripheral insulin resistance from the oral glucose tolerance test (OGTT) data.

Methods

Sample

TONE was a multicenter randomized clinical trial funded by the National Institute of Health (NIH) to examine the effect of two nonpharmacologic interventions (weight loss and/or low sodium diet) in maintaining the normotensive state in elderly persons, aged 60 to 80 years, with essential hypertension, who were withdrawn from antihypertensive medication 90 days after the start of intervention. By a priori study design, TONE recruited both an obese and a nonobese cohort for the study (67% vs 33%, respectively), who were healthy and ambulatory (17,18). The TONE study excluded persons with cancer or a psychiatric illness in the last 5 years, persons who had a stroke or an acute myocardial infarction in the past 6 months, persons with a history of congestive heart failure, persons with chronic obstructive pulmonary disease or valvular heart disease, diabet-
ics who were using insulin, and persons with fasting hyperglycemia. The site-specific ancillary study described in this report began after the first wave of randomized participants had started the TONE intervention. Therefore, persons in the first wave were not approached to participate in the ancillary study because it was no longer possible to obtain preintervention laboratory samples. Persons were also excluded from participation in this ancillary study if they had a history of diabetes mellitus. A separate informed consent was obtained from all ancillary study participants.

**Measurements**

A baseline OGTT was obtained immediately after randomization in the TONE study on the ancillary study participants. This occurred prior to the beginning of the TONE intervention and before withdrawal of the antihypertensive medication. Participants were instructed to ingest a high carbohydrate diet for 3 days and to fast for 12 hours immediately prior to the OGTT. A fasting blood specimen was obtained at time 0. Participants were given a standardized 75-g glucose solution and blood specimens were obtained 30, 60, 90, and 120 minutes after ingestion. Glucose, insulin, and C-peptide levels were measured at all time intervals. Glucose was measured using a glucose oxidation method. Insulin levels were measured using a monoclonal antibody microparticle enzyme immunoassay kit on an IMX instrument (normal insulin range 0–22.7 μU/mL) (19; Abbott, Tokyo, Japan). The interassay coefficient of variation for the insulin measurements ranged from 3.4 to 4.5% and the intraassay coefficient of variation ranged from 2.5 to 4.0%. This insulin assay shows no cross-reactivity with proinsulin (<0.005%) (19). C-peptide levels were measured by a radioimmunoassay (RIA) method (20; Diagnostic Productions, Los Angeles, CA). A fasting lipid profile was also collected. Total cholesterol, HDL, and triglycerides were measured using an enzymatic method on the Technicon DAX analyzer. Low density lipoprotein (LDL) was calculated using the Friedewald equation (21).

At the baseline ancillary study visit height, weight, demographic information, past medical history, and current medication use were also collected using a standardized protocol. Hip circumference was measured using an anthropometric tape at the level of the maximal protrusion of the gluteal muscles. Waist circumference was measured at the level of the umbilicus. The waist/hip ratio was reported as a measure of central obesity (22). Three blood pressure readings were measured by trained personnel after the participant had been seated for 5 minutes, according to the Trials of Hypertension Prevention (TOHP) protocol, using a standard mercury sphygmomanometer (23).

The criteria used in this ancillary study to categorize glycemic states were recommended by the World Health Organization (WHO) (24). The criteria used to categorize persons into lipid groups were recommended by the National Cholesterol Education Program (NCEP) (25). The method used in this ancillary study to estimate beta cell function (corrected insulin response or CIR) and peripheral insulin resistance (insulin activity or A) from the OGTT data has been described by Sluiter and colleagues (26,27). Decreasing CIR values indicate decreasing beta cell function and decreasing A values indicate increasing peripheral insulin resistance (26,27). Area under the curve (AUC) for glucose, insulin, and C-peptide was calculated using the trapezoid method (28).

**Statistical Analysis**

Descriptive and inferential statistical analyses were performed using SPSS and Epi Info, version 6 (29,30). One-way analysis or chi-square, as appropriate, were used to compare glycemic status group with participant demographic characteristics (Table 1), with fasting laboratory values (Table 2), and with glucose, insulin, and C-peptide AUC data (Table 4). Glycemic status groups were compared before and during the OGTT using Scheffe post hoc comparisons, following one-way analyses of variance of glucose, insulin, and C-peptide data. These data were also analyzed using repeated-measures analysis of variance of postbaseline gain scores to assess group effect, time effect, and group-by-time interaction during the OGTT. One-way analysis of variance was used to compare beta cell function (CIR) and peripheral insulin resistance (A) among glycemic status groups (Table 3). All assessments of statistical significance were two-tailed, with the criterion for statistical significance set at the .05 level.

### Table 1. Glycemic Status by Baseline and Demographic Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (N=95)</th>
<th>NGT (n=43)</th>
<th>IGT (n=41)</th>
<th>NIDDM (n=11)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>65.4 ± 4.2</td>
<td>65.7 ± 4.1</td>
<td>65.1 ± 4.4</td>
<td>65.2 ± 3.5</td>
<td>.824</td>
</tr>
<tr>
<td>Race (Caucasian)</td>
<td>78 (82.1)</td>
<td>34 (79.1)</td>
<td>36 (87.8)</td>
<td>8 (72.7)</td>
<td>.400</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>47 (49.5)</td>
<td>20 (46.5)</td>
<td>20 (48.7)</td>
<td>7 (63.6)</td>
<td>.594</td>
</tr>
<tr>
<td>Education (year)</td>
<td>13.7 ± 2.1</td>
<td>13.4 ± 1.9</td>
<td>13.9 ± 2.3</td>
<td>13.9 ± 2.8</td>
<td>.525</td>
</tr>
<tr>
<td><strong>Physical Examination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.0 ± 3.4</td>
<td>29.6 ± 3.5</td>
<td>30.1 ± 3.2</td>
<td>31.3 ± 3.7</td>
<td>.305</td>
</tr>
<tr>
<td>Systolic BP‡</td>
<td>135.6 ± 13.7</td>
<td>133.3 ± 14.5</td>
<td>136.5 ± 13.6</td>
<td>141.4 ± 8.3</td>
<td>.186</td>
</tr>
<tr>
<td>Diastolic BP‡</td>
<td>80.9 ± 7.6</td>
<td>80.3 ± 8.0</td>
<td>80.4 ± 6.9</td>
<td>84.9 ± 7.9</td>
<td>.174</td>
</tr>
</tbody>
</table>

*Notes: Values are reported as means ± SD or n (%). NGT = normal glucose tolerance; IGT = impaired glucose tolerance; NIDDM = non–insulin-dependent diabetes mellitus.

*One-way analysis of variance or chi-square, as appropriate.

†Represents the mean of three blood pressure readings (mm Hg) taken prior to the OGTT while participants were still taking their antihypertensive medication.
RESULTS

There were 225 participants randomized in the TONE study from the University of Tennessee, Memphis, site. Forty-nine persons were excluded from the ancillary study because they had already started the TONE study intervention. Five persons were excluded from the ancillary study due to a history of diabetes mellitus, and 76 persons elected not to participate in the ancillary study. Ninety-five persons agreed to participate in the ancillary study, and their baseline data are described in this report.

Baseline demographic characteristics and physical examination findings by glycemic status group are listed in Table 1. The mean body mass index (BMI) expressed in kg/m² was 30.0 ± 3.4. Female participants had a statistically higher BMI than male participants (30.9 ± 3.7 vs 29.1 ± 2.9, p = .011). Defining overweight as a BMI ≥27.8 for males and BMI ≥27.3 for female; 87.2% of female participants and 66.7% of male participants in this ancillary study could be classified as overweight. The mean waist/hip ratio for all participants was 0.96 ± 0.06, and male participants had a statistically higher waist/hip ratio than females (0.98 ± 0.05 vs 0.94 ± 0.07; p = .008). All participants had reasonable blood pressure control at baseline while taking an antihypertensive medication (see Table 1). Thiazide diuretics, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and beta-blockers were the most commonly used medications (38%, 26.3%, 20%, 10.5%, respectively). Type of antihypertensive medication was not associated with glycemic status, insulin, or C-peptide levels in the group as a whole or in subgroup analysis (31).

In this sample of elderly participants with hypertension, 43 (45.3%) had normal glucose tolerance (NGT), 41 (43.2%) had impaired glucose tolerance (IGT), and 11 (11.6%) had undiagnosed non–insulin-dependent diabetes mellitus (NIDDM). Results of the glucose, insulin, and C-peptide values from the 2-hour OGGT for the three glycemic status groups are illustrated in Figure 1. Fasting glucose, insulin, and C-peptide values appear in Table 2. Only five persons had a fasting glucose ≥125 mg/dL, with four persons being in the undiagnosed NIDDM group and one person being in the IGT group. Defining fasting hyperinsulinemia as an insulin value >22.7 μIU/mL (upper limit of normal of the insulin assay used), only one participant had a high fasting insulin level, and this person was in the IGT group (19). One person in the NGT group and one person in the IGT group had fasting insulin levels >17.5 μIU/mL but <22.7 μIU/mL. All other participants had fasting insulin values <17.5 μIU/mL. A repeated-measures analysis of variance of OGGT insulin gain scores documented a nonsignificant between-groups effect (p = .742), a highly significant time effect during the OGTT (p < .001), and a significant Group by Time interaction effect during the OGTT (p = .048). No one-way analysis of variance of insulin or C-peptide data, either fasting or at any follow-up time point during the OGTT, documented a statistically significant difference between glycemic status groups. Of particular interest was the lack of correlation between BMI, waist/hip ratio, triglyceride, or HDL values with glycemic status or with fasting insulin level in the group as a whole or when race- and gender-specific subgroups were examined.

Of this hypertensive elderly cohort, 39% reported a history of elevated lipid levels, but only three persons (3.2%) reported currently taking medications for hyperlipidemia (two on an HMG Co-A reductase inhibitor and one on Gemfibrozil). The mean cholesterol level (mg/dL) for all participants was 202.1 ± 31.5, the mean LDL level (mg/dL) was 131.1 ± 30.0, the mean HDL level (mg/dL) was 45.3 ± 14.7, and the mean triglyceride level (mg/dL) was 160.8 ± 96.7 (see Table 2). The undiagnosed NIDDM group appeared to have a higher mean triglyceride
value as compared to the IGT or NGT groups, but this difference did not reach statistical significance \((p = .334)\). There were no statistical differences in total cholesterol, LDL, or HDL between the undiagnosed NIDDM, IGT, or NGT groups. Based on NCEP guidelines for characterizing persons as having high lipid levels, only 13 (13.7%) had a fasting total cholesterol level \( \geq 240 \text{ mg/dL} \), 17 (17.9%) had an LDL level \( \geq 160 \text{ mg/dL} \), 20 (21.1%) had an HDL \(< 35 \text{ mg/dL} \), and 5 (5.3%) had a triglyceride level \( \geq 200 \text{ mg/dL} \). Four persons had both low HDL and high triglycerides, but there were no statistically significant differences between the glycemic status groups regarding this specific lipid profile associated with syndrome X. Also, the one participant with fasting hyperinsulinemia did not have high triglycerides or low HDL. None of the three patients taking lipid lowering medications had fasting hyperinsulinemia.

We estimated beta cell response (CIR) and peripheral insulin resistance (A) from the OGTT data (see Table 3) using the method of Sluiter and colleagues \((26,27)\). A one-way analysis of variance of the three glycemic status groups’ CIR data was highly significant \((p < .001)\). The mean CIR was highest in the NGT group and lowest in the undiagnosed NIDDM group (see Table 3). A post hoc comparison by the Scheffé method revealed that both the IGT and undiagnosed NIDDM groups had significantly lower CIR means when compared to the NGT group mean \((p < .05)\) (see Table 3). Furthermore, regression analysis documented a highly significant linear trend representing decreasing CIR across WHO glycemic groups with increasing impairment of glycemic control, suggesting that beta cell function decreased with increasing glycemic impairment \((B = -0.38, p < .001)\). One-way analysis of variance of peripheral insulin resistance, the A index, was statistically significant. However, post hoc analysis using the method of Scheffé revealed no significant difference between the mean of any individual subgroup when compared to the mean of any other individual subgroup, which established that the significant omnibus test resulted from subgroup differences that attained statistical significance only by combining the subgroups or otherwise increasing statistical power. In addition, there were no statistically significant differences in the mean CIR or mean A values when we examined racial, gender, or weight groupings in our data set.

We estimated AUC by the trapezoidal method from the OGTT data for glucose, insulin, and C-peptide values (see Table 4). A one-way analysis of variance of the three glycemic status groups’ glucose AUC data was highly significant \((p < .001)\). The mean glucose AUC was highest in the undiagnosed NIDDM group, intermediate in the IGT group, and lowest in the NGT group (all \(p < .05\) by post hoc comparisons). There were no statistically significant differences in the mean AUC for insulin or C-peptide data in the three glycemic status groups (see Table 4).

**DISCUSSION**

The data demonstrate that undiagnosed NIDDM and IGT are common in elderly persons who are being treated for essential hypertension even after persons known to have diabetes and persons with fasting hyperglycemia have been excluded from the study sample \((31)\). This finding is similar to previous research from the National Health and Nutrition Examination Survey (NHANES) II study regarding the high prevalence of undiagnosed diabetes in the general population \((2)\). However, the study cohort did not have a high prevalence of hypertriglyceridemia despite the high prevalence of impaired glycemic control and obesity.

The data also reveal that the majority of study participants did not have fasting hyperinsulinemia and appeared not to have peripheral insulin resistance as estimated by the Sluiter methods, despite the high prevalence of obesity. This is in contrast to previous research that has demonstrated that hypertension and obesity are associated with hyperinsulinemia and peripheral insulin resistance \((9,32)\). Our study also revealed that persons in the IGT and NIDDM groups appeared to have a delayed insulin response to the glucose challenge compared to persons in the NGT group, as evidenced by the significant Group by Time interaction of the OGTT insulin data. Further, the estimate of beta cell function (CIR) was lower in the NIDDM and IGT groups than in the NGT group, as evidenced by the significant Group by Time interaction of the OGTT insulin data.
groups compared to the NGT group. These facts taken together suggest that impaired beta cell function with decreased insulin levels plays a more prominent role in the etiology of the impaired glycemic control in our study participants, rather than peripheral insulin resistance leading to hyperinsulinemia. Therefore, we believe our data suggest that peripheral insulin resistance leading to hyperinsulinemia may not be a major etiologic determinant of hypertension or impaired glycemic control in certain groups of elderly persons.

There are a number of factors that may account for our divergent findings from previous reports. Many previous studies may have used an insulin assay that cross-reacts with proinsulin, leading to a situation where insulin values are artifically elevated due to high levels of circulating proinsulin (33–35). Thus, use of an insulin assay that cross-reacts with proinsulin has the potential to create an association between hypertension and hyperinsulinemia when none may exist. Our study used an insulin assay based on a monoclonal antibody that does not cross-react with proinsulin. Therefore, we believe our measurement of insulin values is more specific and that our hypertensive participants did not exhibit hyperinsulinemia, despite the fact that a large number had impaired glycemic control and were obese.

Our study findings may also differ from previous reports due to differences in the demographic composition of the study participants. Previous research has found an association between hypertension and hyperinsulinemia in groups with a younger average age than in our study cohort (32). Consequently, one may speculate that peripheral insulin resistance and hyperinsulinemia may be a primary etiologic pathway in the development of impaired glycemic control and hypertension in younger age groups, whereas beta cell failure may be a primary etiologic pathway in the development of impaired glycemic control in older age groups. Thus, the comparison of studies with different age groups would yield differing results in regards to the association between hyperinsulinemia and hypertension. An alternative hypothesis that may explain our findings is decreased survivorship of persons with hyperinsulinemia and syndrome X.

We acknowledge that our study has several limitations. Our study did not directly measure peripheral insulin resistance or beta cell function, but estimated it by examining the fasting insulin levels and calculating it with the method of Sluiter and colleagues. However, as fasting insulin is a relatively reliable indication of a hyperinsulinemia or insulin resistance state (36,37), our data support a lack of either in our study cohort. Nevertheless, we believe it is important to repeat our observations in a larger study cohort where more direct measures of beta cell function and peripheral insulin resistance can be made. Another limitation of our study is that our results may be confounded by the recruitment process of the original TONE study. By study design the TONE study recruited elderly participants so that at least 67% would be obese and excluded certain persons with diabetes. Although the exact overall effect of the TONE recruitment process on the ancillary study results cannot be known, we would have expected it to generate a cohort with a high prevalence of hyperinsulinemia, peripheral insulin resistance, and syndrome X due to the high prevalence of obesity and hypertension in the study cohort. However, this is not what our data analysis revealed. We also acknowledge that our results may be confounded by the fact that all our study subjects were currently taking an antihypertensive medication. Although previous research has revealed that certain medications can affect glycemic status either positively or negatively, in our study, type of medication was unrelated to glycemic status or insulin level (31). Thus the potential for generalization of our findings to groups who are not elderly, predominantly obese, or hypertensive is limited. Therefore, it is important to repeat our observations with a larger elderly study population.

In conclusion, our data suggest that beta cell dysfunction is the primary reason that certain elderly individuals with hypertension in our cohort had impaired glycemic control and others did not. Recognizing that persons with syndrome X have peripheral insulin resistance, hyperinsulinemia, and certain lipid abnormalities in addition to hypertension and impaired glycemic control, we believe our data support the conclusion that the study cohort essentially did not have this disorder (12). However, we believe that further research is needed to elucidate these relationships using methods that more directly measure beta cell function and peripheral insulin resistance. Further, as syndrome X with its associated peripheral insulin resistance has been postulated to play a crucial role in the development of coronary artery disease (CAD), we believe that it is important to characterize the CAD experience of elderly persons with hypertension, central obesity, and glucose impairment, but who do not appear to have syndrome X (12,16,38).

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Address correspondence to Karen C. Johnson, MD, MPH, Department of Preventive Medicine, 66 N. Pauline, Suite 600, University of Tennessee, Memphis, TN 38163. E-mail: kjohnson@utmem1.utmem.edu

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